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Criteria for Determining Disability in Infants and Children: Low Birth Weight

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

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Structured Abstract

Objective. The Social Security Administration (SSA) of the Department of Health and Human Services requested that the Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Center (EPC) program, produce an evidence report to determine whether specific factors or combination of factors alone or in addition to birth weight predict significant developmental disability in former premature infants and whether premature infants with such factors have long-term developmental disabilities.

Search Strategy. Studies with original data used in this evidence report were identified through MEDLINE® searches of the English language literature published between 1966 and January 2002. Additional studies were identified from supplemental searches in ERIC, PsycInfo, HealthStar and Embase and from reference lists, review and primary articles, and from domain experts.

Selection Criteria. We reviewed retrospective and prospective studies reporting impairments in infants or children who weighed 2,000 grams or less, whose gestational age was 35 week or less, or whose birth weight or gestational age were below these thresholds. Preferences were given to recent studies and studies with a minimum of 6 months of follow-up.

Data Collection and Analysis. We incorporated 178 English language articles in the evidence report. Relevant data from each article were abstracted into evidence tables. Information from the evidence tables was synthesized into summary tables describing the findings of each study. Studies were graded according to the methodological quality and applicability.

Main Results. We looked for evidence of association of very low birth weight (VLBW defined as <1500 grams) with six outcome conditions. The evidence of the literature overwhelmingly supports that the risk of cerebral palsy (CP) and major neurologic disability is increased among VLBW infants compared to full-term infants. The literature is consistent in demonstrating that risk of CP, major neurosensory and/or neurologic disability is inversely proportional to the degree of immaturity whether measured by gestational age or by birth weight.
The evidence demonstrates that children who were born VLBW have significantly higher rates of cognitive abnormality in early childhood and a several-fold increased prevalence of IQ <70 as adults compared with children or adults who were born normal birth weight at term. There is evidence that even children who were apparently "well" VLBW infants during their neonatal course are also at significantly greater risk for both moderate and severe delay compared to larger birth weight groups.

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. All of the above problems have been identified in disproportionate numbers in the VLBW infants.

The studies provided strong evidence of increased incidence of speech and language delays in VLBW and extremely premature infants, and identified clinical factors associated with the increased incidence. Across all measures of short-term memory and language outcomes,

preschool children who were born preterm performed at a lower level than children who were full-term counterparts. These deficits were independent of the general IQ.

The evidence identified by this review clearly demonstrates that children born as VLBW infants, with or without retinopathy of prematurity (ROP), are at significantly increased risk of visual impairments and disability compared to children born full term. The risk of visual disability in VLBW infants varies inversely with gestational age.

The studies reviewed indicate that VLBW infants with bronchopulmonary dysplasia (BPD) are at increased risk for long-term pulmonary disability. The greater the severity of BPD, the greater is the association with long-term pulmonary impairment and need for re-hospitalization.

VLBW infants, with or without other conditions, are at high risk for poor growth during the first years of life due to acute neonatal illnesses, developmental delays, and chronic illnesses.

Conclusions. Surviving premature infants often sustain multi-organ system complications that may persist beyond the first few years of life and frequently result in permanent impairments. Complications of even a single organ system may have a profound impact upon other organ systems. Biomedical determinants of disability in premature infants are often compounded by adverse determinants of social and psychological adaptation of these vulnerable children and their families.

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Summary

Overview

The Social Security Administration (SSA) of the Department of Health and Human Services requested that the Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Center (EPC) program, produce an evidence report to determine whether specific factors or a combination of factors alone or in addition to birth weight predict significant developmental disability in former premature infants and whether premature infants with such factors have long-term developmental disabilities. This evidence report is prepared to assist the SSA in updating its *Listing of Impairments*, and revising its disability policy, as may be appropriate. This report does not provide or suggest a new listing of impairments.

This report examines the evidence that Very Low Birth Weight (VLBW) in infants (birth weight <1,500 grams) with or without other conditions is associated with long-term disabling outcomes. The primary outcomes of interest included in this report are cerebral palsy (CP), mental retardation (MR), hearing/speech/language/behavioral impairments, visual impairments, adverse pulmonary function, and disrupted growth.

The category of VLBW infants was chosen because it is well recognized to represent a population of infants, primarily premature infants, at increased risk for acute and chronic impairments related to their immaturity. VLBW is often divided into subcategories of lower birth weights, such as less than 1,250, less than 1,000, and less than 750 grams, to facilitate analyses of infants within different birth weight strata. Extremely Low Birth Weight (ELBW) infants are often defined as infants with birth weight less than 1000 grams, although this definition may vary among studies by as much as 250 grams in either direction. In general, the lower the birth weight, the greater the degree of immaturity, and the greater the risk for serious complications.

Birth weight, however, is not a perfect measure of immaturity since some infants may have birth weights that are disproportionately large or small for their gestational age. Many studies appropriately and preferably use gestational age as the marker of prematurity. Similar to birth weight, gestational age categories of premature infants often include groupings of premature infants less than 32 weeks gestation, less than 30 weeks gestation, less than 28 weeks gestation; or less than 26 weeks gestation. Less than 32 weeks gestational age is considered by some authorities as "very premature" and less than 28 weeks gestational age as "extremely premature."

Premature birth is an important public health problem due to the number of premature births each year, the serious acute complications of prematurity, and the long-term sequelae directly related to the vulnerability of VLBW infants. Among the four million births in the United States during the year 2000, about 58,000 (1.4%) were VLBW (<1,500 grams). Although VLBW is a relatively small proportion of total births in the USA, this category of infants accounts for the highest neonatal mortality and greatest morbidity among newborns. The long-term complications result in significantly increased tangible and intangible lifelong costs to the family and society for medical care as well as for ongoing ancillary health and educational services.

Advances in neonatal/perinatal medicine have improved the survival and the quality of survival

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of premature infants. Despite advances in medical care, infants born prematurely experience a disruption in the normal process of growth and development. The degree of disruption in the growth and development of each organ system is a reflection of the degree of immaturity and physiologic derangement. Survival is inversely proportional to the degree of prematurity. Recent evidence indicates that approximately 95 percent of infants with birth weights between 1,251 and 1,500 grams survive in contrast to approximately 75 percent of infants with birth weight less than 1,250 grams. For any adverse sequela associated with premature birth, the incidence as well as the severity of the complication is inversely proportional to the gestational age. For instance, 12 percent of infants with birth weight between 1,251 and 1,500 grams survived with at least one major morbidity in contrast to 53 percent with birth weight 501 to 1,250 grams.

Surviving premature infants often sustain multi-organ system complications that may persist beyond the first few years of life and frequently result in permanent impairments. Examples include major neurodevelopmental impairments, such as CP, MR, deafness and disorders of speech/language/communication; perception, attention, behavior and learning disorders; blindness or other visual impairments; chronic lung disease; and growth retardation. Complications of even a single organ system may have a profound impact upon other organ systems. Biomedical determinants of disability in premature infants are often compounded by adverse determinants of social and psychological adaptation of these vulnerable children and their families.

Reporting the Evidence

Key questions of interest

This review addresses the following key questions of interest to SSA.

For infants with birth weight <1,200 grams and for infants with birth weights between 1,200 grams and 1,500 grams:

1. What factors or combination of factors alone or in addition to birth weight will predict significant developmental impairment in former premature infants?
2. Are such infants developmentally impaired at 1 year, 2 years, or beyond?

In order to identify the functional or physical outcomes related to disability and the elements that predicted them, we sought evidence that a specific factor was significantly associated with a specific disability (e.g., very low birth weight infants with bronchopulmonary dysplasia [BPD] have lower receptive language scores; or the degree of immaturity influences the risk of CP and neurodevelopmental disability in VLBW infants). We looked for evidence of association of VLBW with six outcome conditions:

- CP and neurological impairments
- Abnormal cognitive development and MR
- Speech/language delay, hearing loss, behavioral disorders, and learning disabilities
- Visual impairment (with or without other conditions)
- Pulmonary impairment (with or without other conditions)
- Growth impairment

Methods

A systematic literature search was performed for journal articles with original data. English language studies were identified primarily through MEDLINE® searches conducted between October 2000 and February 2001. We performed an updated search in September 2001 and again in January 2002. Supplemental searches were also performed in ERIC, PsychINFO, HealthSTAR and E<BASE. Additional studies were identified from reference lists, review and primary articles, and from domain experts and reviewers.

Disability is not a specific medical condition that can be readily searched for. Thus we had to look at many studies with related concepts (i.e., medically definable impairments that are related to disability) to identify potentially relevant studies. Therefore, we developed a comprehensive list of predictors and outcomes by organ system and those that are associated with VLBW infants. The predictor and outcomes then formed the basis of literature search terms.

We focused the literature review primarily on premature infants born weighing less than 1,500 grams, including all subcategories of birth weights (e.g., less than 1,250 grams, less than 1,000 grams, and less than 750 grams). We also incorporated literature that included infants with birth weight less than 1,500 grams within a larger premature cohort and literature on infants whose prematurity was defined by gestational age, since many studies use gestational age and not birth weight criteria.

We reviewed retrospective and prospective studies reporting impairments in infants or children who weighed 2,000 grams or less, whose gestational age was 35 weeks or less, or whose birth weight or gestational age were below these thresholds. Longitudinal data for a minimum of 6 months was preferred.

We identified and screened 16,614 abstracts from the literature searches. These abstracts covered 13 categories: central nervous system (2,930 abstracts), opthalmology (398), audiology (80), pulmonary (1,833), nutrition and growth (2,533), medication (dexamethasone) (183), perinatal factors (875), illness acuity (56), infectious diseases (2,378), gastrointestinal (477), bone/osteomalacia (10), health care (466), and immune disorder (921). Approximately 1,693 potentially relevant articles were retrieved after screening the abstracts.

The very large number of articles precluded all of them from being incorporated into the evidence report. We used the following method to reduce the articles to a feasible number and include the most relevant. We screened in articles that met the minimum inclusion criteria for LBW, reported one or more relevant clinical outcomes, had a followup duration greater than or equal to 6 months, a study size greater than 10, and enrolled patients born after 1980. We then established a hierarchy of studies based on study size and birth year of the infants. Studies with birth years from 1990 onward were given preference, followed by studies with birth years between 1985 and 1989, and then studies before 1985. Within each birth year cohort, studies with more than 100 infants were selected first, followed by studies with 50 to 100 infants and less than 50 infants. Using this classification hierarchy, we worked through the most relevant (recent) and strongest (largest study size) studies in succession before older and smaller studies, until a complement of 178 articles were reviewed.

We report the evidence organized by the six outcome conditions listed under the key questions. We summarized the evidence in three complementary forms. The evidence tables provide detailed information about the features of study design and results of all the studies reviewed. A narrative and a tabular summary of the strength and quality of the evidence of each study are provided for each outcome condition. The summary tables describe the strength of the evidence according to four dimensions: study size, applicability of the study population, association of the factor of interest with impairments, and the methodological quality of the study.

Findings

Evidence that VLBW With or Without Other Conditions is Associated With Cerebral Palsy (CP) and Neurologic Disability

The literature overwhelmingly supports evidence that the risk of CP and major neurologic disability is increased among VLBW infants compared to full-term infants. The literature is consistent in demonstrating that risk of CP, major neurosensory and/or neurologic disability is inversely proportional to the degree of immaturity whether measured by gestational age or by birth weight. The recently reported incidence of CP is currently stable compared to the 1980s (7-10 percent VLBW infants; 7-17 percent ELBW infants) or modestly decreased despite improved survival of extremely immature infants. This suggests that recent advances in neonatal care have had either no or modest effect on further reduction in the incidence of CP. Several studies demonstrated that the risk of major neurosensory or neurologic disability may range from 12-50 percent among VLBW and ELBW infants. Despite the stable risk of CP, the risk of disability, due primarily to visual disabilities, has increased since the 1980s. Differences among studies regarding the incidence of CP, neurologic, and neurosensory disability may be accounted for by differences in the criteria for neurologic/neurosensory disability, the era of study, the degree of immaturity, and other characteristics or risk factors of the patient population, neonatal care practices, as well as length and completeness of followup.

Several articles in this review provide compelling evidence that cerebral white matter damage (WMD), as manifested by periventricular leukomalacia (PVL) (such as echodensities and echolucencies), ventriculomegaly, posthemorrhagic cerebral infarct, and severe intracranial hemorrhage are among the strongest predictors of CP and other neurologic disabilities in VLBW infants. Visual and ocular abnormalities are often associated with neurodevelopmental abnormalities in VLBW infants with cerebral white matter damage. The degree of visual impairment correlates with the degree of neurodevelopmental impairment.

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, fetal hypoxia/acidosis, and premature rupture of membranes (which may be related to antenatal inflammation and infection) and abruption appear to play an important role via stimulating a fetal inflammatory response that injures the immature cerebral white matter.

Several studies documented that prolonged mechanical ventilation and BPD are associated with increased adverse neurodevelopmental outcome in premature infants compared to infants without BPD or prolonged mechanical ventilation. 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. The evidence supports that BPD and systemic dexamethasone each may be separate factors influencing the risk of CP and neurologic impairment in VLBW infants.

Studies also illustrate that VLBW infants with parenting, social, and environmental risk factors are at increased risk for neurodevelopmental disabilities. 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 synergistic effects on an infant's outcome.

Evidence that VLBW With or Without Other Conditions is Associated With Abnormal Cognitive Development and Mental Retardation (MR)

The evidence demonstrates that children who were born VLBW have significantly higher rates of cognitive abnormality in early childhood and a several-fold increased prevalence of IQ <70 as adults compared with children or adults who were born normal birth weight at term. Given current rates of birth and

VLBW in the USA, these results suggest that there may be more than 3,500 new cases of MR in the United States each year in former VLBW infants. There is evidence that even children who were apparently "well" VLBW infants during their neonatal course are also at significantly greater risk for both moderate and severe delay compared to larger-birth-weight groups.

Among children born as ELBW infants, the prevalence of MR is even higher than in VLBW infants, who are larger than ELBW infants. Approximately 40 percent of ELBW survivors have Bayley Mental Development Index (MDI) <70, half of ELBW survivors have at least one significant neurodevelopmental impairment, and 20-35 percent of ELBW survivors have two or more impairments. Evidence suggests that the incidence of MR in ELBW infants is not changing with time, despite recent increases in survival rates in this birth weight category. Our search methods identified evidence that birth weight is a useful factor in identifying VLBW infants at especially high risk for MR. However, once the range of birth weight and gestational age are narrowed to the most immature infants, and stronger predictors of neurodevelopmental outcome are taken into consideration, the evidence that birth weight or gestational age is useful in identifying VLBW infants at high risk for MR was mixed.

Intraventricular hemorrhage (IVH), particularly severe (i.e., grade III or IV) IVH, PVL, and ventriculomegaly are also among the strongest independent predictors of cognitive impairment and MR in VLBW and ELBW infants. Infants with a combined outcome IVH ≥ grade III or PVL are more than twice as likely to have Bayley MDI <70 as those without these findings, after adjusting for the effect of other clinical factors.

Recent studies strongly document a significant independent relationship between BPD and abnormal neurodevelopment in both VLBW and ELBW infants. This effect of BPD on long term outcome is independent from the many co-morbid conditions commonly seen concurrently in VLBW infants, such as intraventricular hemorrhage, posthemorrhagic hydrocephalus and periventicular leukomalacia. Evidence strongly indicates that postnatal systemic steroid therapy (dexamethasone) for the amelioration or prevention of BPD is an independent determinant of abnormal cognitive development in ELBW infants after adjusting for clinical factors and associated with almost two-fold increased risk of Bayley MDI <70.

Our search methods identified many strong studies documenting a significant independent association between parenting-pychosocial risk factors and cognitive development in VLBW infants even after accounting for the effects of intraventricular hemorrhage and chronic lung disease. Methods used to measure social risk are numerous, however, and the identified evidence in the literature 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. The quality of parent-infant interactions may play an important role in cognitive development of VLBW infants. The variability among studies with respect to the association of parenting-pyschosocial 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.

The identified evidence suggests that race may be an independent predictor of cognitive development in VLBW infants with black race among the social risk factors associated with an approximately 50 percent increased risk of subnormal Bayley MDI.

The level of maternal education was identified as a significant independent predictor of abnormal cognitive development in VLBW and ELBW infants. One methodologically strong study found that maternal education less than high school graduate level increased risk of Bayley MDI <70 almost two-fold.

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.

Evidence suggests that illness severity scoring systems may be useful in identifying infants at risk for MR. 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.

The evidence identified by our search methods was equivocal regarding the utility of antepartum and intrapartum factors as independent predictors of MR. Strong studies suggested that specific antepartum factors (e.g., use of antenatal steroids, maternal hypertension, route of delivery, or inborn versus outborn) do not provide a useful contribution to prediction of MR in ELBW infants after accounting for other clinical factors.

The identified evidence regarding intrauterine growth retardation/small for gestational age (IUGR/SGA) as an independent risk factor for MR was equivocal. One study documented worse cognitive development in children who were SGA VLBW infants compared with appropriate gestational age (AGA) VLBW infants. Other studies that found that SGA ELBW infants were not at increased risk for cognitive delay compared with their AGA peers after adjusting for other clinical factors.

Our methods located no studies examining the relationship between necrotizing enterocolitis (NEC) and subsequent cognitive development in VLBW infants.

Our search methods identified studies that examined the relationship between sepsis or meningitis and subsequent cognitive development in VLBW infants. Two studies found that neither sepsis nor meningitis was associated with cognitive outcome in ELBW infants after adjusting for other clinical factors.

Evidence that VLBW is Associated With Speech/Language Delay, Hearing Loss, Behavioral Disorders, and Learning Disabilities

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. All of the above problems have been identified in disproportionate numbers in the VLBW infants.

The studies provided strong evidence of increased incidence of speech and language delays in VLBW and extremely premature infants, and identified clinical factors associated with the increased incidence. One study emphasized higher prevalence of functional limitations in most language domains with children who were born ELBW. Children who were ELBW have a higher utilization rate of speech therapists and require more educational and health care services. Across all measures of short-term memory and language outcomes, preschool children who were born preterm performed at a lower level than children who were full-term counterparts. These deficits were independent of the general IQ.

In overall communication skills, children who had BPD as preterm neonates scored significantly lower than the other comparison non-BPD groups. Even after controlling for lower IQ, children who were VLBW infants with BPD have lower receptive language scores.

Data on the incidence of hearing loss in ELBW infants is conflicting. Four excellent, recent studies report higher incidence ranging from 9 to 14 percent and nine studies report rates (~1-2 percent) similar to their full-term controls. This variability may be due to differences in testing methods.

There is good evidence that VLBW infants have increased attention problems and more passive temperament. Intracranial lesions, CP, impaired cognition, and urban socioeconomic setting was associated with the increased incidence.

Available evidence suggests that VLBW and ELBW infants are at higher risk for developing learning disabilities and have difficulty in school. Studies of school learning problems at 6 years may be too early and may miss children with less grossly obvious difficulties.

One study provided evidence that even seemingly "healthy" premature infants may have later sequelae needing special assistance. The well-preterm group, compared to full-term controls, had significantly higher than expected incidence of minimal brain dysfunction including attention deficit disorder, learning disabilities, language impairment, mild neurologic impairment, and general school concerns. In fact, only 25 percent had no concerns by grade 5 compared to 57 percent in term controls. The mother's perception of their infants' competence was a sensitive marker for disabilities.

Evidence that VLBW With or Without Other Conditions is Associated With Visual Disability

The evidence identified by this review clearly demonstrates that children born as VLBW, with or without retinopathy of prematurity (ROP), are at significantly increased risk of visual impairments and disability compared to children born full term. The risk of visual disability in VLBW infants varies inversely with gestational age. The risk of having any ophthalmic morbidity (e.g., significant reduction in visual acuity tests or presence of strabismus, myopia, color vision defect, or visual field defect) is two-fold greater in children born VLBW infants and five-fold greater in children born ELBW compared to children born at term. Ophthalmic morbidity (i.e., greatest reduction in visual acuity or incidence of strabismus, myopia, etc.) is highest in eyes with severe (Stage 3 or 4) ROP. No or regressed mild ROP, by itself, has no major important long-term effect on visual acuity, although children born prematurely with no or regressed mild ROP may have statistically significantly reduced visual acuities compared with full-term controls.

The risk of blindness is higher in ELBW infants compared to normal birth weight controls and is inversely related to birth weight or gestational age. The reported incidence of blindness in ELBW infants, the population at greatest risk for visual disability, ranges from 1 to 4 percent in most studies identified in this review.

Retinal ablation with cryotherapy or laser therapy for severe (i.e., threshold) ROP significantly reduces 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 percent of treated eyes). Unfavorable outcome was particularly true in eyes with Zone 1 (posterior pole) threshold ROP regardless of whether or not the eye received cryotherapy (i.e., poor outcome in 75 percent of Zone 1 treated eyes and 92 percent of not treated eyes). 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. Retinal ablative therapy (cryotherapy or laser therapy) for threshold ROP is cost effective therapy that can improve the quality of life. Laser therapy can reduce the risk and/or severity of myopia, which is a major complication of premature infants, especially in premature infants with severe ROP. Any reduction in myopia is important in terms of long-term visual benefit.

A 10-year followup of premature infants with threshold ROP revealed that the rate of retinal detachment among control (no cryotherapy) threshold eyes increased at 5.5 years (38.6 percent) and again at 10 years of age (41.4 percent), after having been "stable" during the first 3 years of followup. The rate of retinal detachment remained stable in treated eyes (22.0 percent). Eyes with severe ROP and not treated, have smaller visual fields compared to eyes that never had ROP. Eyes treated with cryotherapy had a further reduction in the visual fields. 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.

VLBW infants are also at increased risk for non-retinal ophthalmic diseases. Cortical visual impairment is visual impairment due to central nervous system (CNS) damage. 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, ventriculomegaly, intracranial hemorrhage, and posthemorrhagic hydrocephalus. Neuroimaging of VLBW infants via cranial ultrasonography, cranial tomography, 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. The strong association of visual impairment with the extent of MRI evidence of cerebral white matter damage and the concomitant occurrence of neurodevelopmental disability in premature infants is well documented.

One study demonstrated that even healthy preterm children with no detectable neurodevelopmental problems on screening examinations, have evidence of visual-motor disabilities when these functions are specifically tested.

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. Myopia is the most common ophthalmic sequela of premature infants and requires optical correction. Other adverse ophthalmic outcomes, such as astigmatism and anisometropia, were highly correlated with severe myopia. Studies clearly illustrate 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.

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. 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. Strabismus may continue to increase in frequency through second year. Among children with Grade III or IV IVH, 100 percent had strabismus (esotropia).

Ophthalmic examinations revealed that premature infants with BPD and no detectable severe neonatal neurological abnormalities and no ROP > Stage 2 had greater incidence of strabismus and high refractive error and poorer recognition acuity compared to premature infants with hyaline membrane disease but no BPD and healthy preterm infants. Extremely premature infants treated with systemic dexamethasone therapy for BPD had significantly higher rates of blindness in addition to significantly higher rates of CP and lower intelligence quotients. Extreme prematurity, brain injury, ROP, BPD, and glucocorticoid therapy individually and/or collectively have an impact on visual disability.

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 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

The studies reviewed indicate that VLBW infants with bronchopulmonary dysplasia (BPD) are at increased risk for long-term pulmonary disability. The greater the severity of BPD, the greater the association with long-term pulmonary impairment and need for re-hospitalization. Children who were VLBW infants who had no BPD have comparable pulmonary outcome to children who were born full term. Children who were VLBW with more severe BPD may have persistent lung disease during young childhood and continuing through to their adolescent, and young adult years. Findings in five studies indicate that BPD at 36 weeks corrected gestational age is predictive of longer-term pulmonary disability through at least 1-2 years of age.

Preterm children with BPD have an increase in multiple measures of pulmonary disability. The most frequently described consequences of pulmonary disability are increased respiratory symptoms and respiratory illnesses, the need for respiratory medications, and re-admission to the hospital for other medical and surgical reasons. Respiratory illnesses frequently documented in children who had BPD include chronic lung disease, recurrent bronchitis and pneumonia, increased airway responsiveness and asthma. Asthma or

bronchial responsiveness actually appears to be increased in VLBW premature children who did or did not have BDP.

Rehospitalization of former VLBW infants is unfortunately a common event especially during the first 2 years of life and is even higher among VLBW infants with BPD. Most hospitalizations are for respiratory conditions or failure to thrive.

Evidence that VLBW With or Without Other Conditions is Associated With Growth Impairment

VLBW infants, with or without other conditions, are at high risk for poor growth during the first years of life due to acute neonatal illnesses, developmental delays, and chronic illnesses (e.g., BPD, gastroesophageal reflux, short-gut syndrome). Understandably, the degree of prematurity and severity of the illness/hospital course have great impact and influence growth. 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. There is evidence that the weight and height of VLBW infants is significantly behind that of normal birth weight infants through 14 years of age, although the differences become less over time.

It is well documented that VLBW infants with BPD are smaller and have difficulty gaining weight while in the neonatal intensive care unit. Recurrent illness and pulmonary exacerbations of BPD, increased metabolic needs and inadequate nutrient intakes all contribute to compromise growth in VLBW infants with BPD. BPD infants with home oxygen therapy had a three-fold increase in rehospitalization for failure to thrive. The primary reasons for failure to thrive in the BPD patients were related to poor feeding and gastroesophageal reflux.

Future Research

We propose two prospective health service research opportunities. The first proposal, "Evaluation of the Application Process of SSA VLBW Disability Criteria," involves documentation of baseline risk factor data on all VLBW infants born within participating regions, following surviving VLBW infants over pre-specified time with respect to pre-specified disabilities, documenting the proportion of VLBW who come to the attention of SSA, relative to the entire regional cohort of VLBW infants, and identifying barriers to referring infants to SSA. This research proposal would help SSA assess the application of SSA VLBW Disability Criteria. This would, in turn, provide greater insight into reasons for successful programmatic implementation and impediments of applying the criteria. It would provide insight regarding the effectiveness of identifying high-risk VLBW infants.

The second proposal, "Determining the Appropriateness of the New VLBW Disability Criteria" proposed by SSA based on the evidence of this report, is a natural next step linked to the first research concept. The combination of these two concepts affords the SSA the ability to know if the process and the criteria are achieving the objectives established by the SSA.

Refinement of predictors of disability or identification of new predictors, and development of a robust, well-designed, and carefully validated predictive models to be used at the time of hospital discharge could create a "profile" of a VLBW infant at risk for specific disabilities. A series of models predictive of longer-term outcome could be developed and validated to incorporate new factors and information noted during specified times of followup. Refinement of risk factors invites a systematic, collaborative effort to develop a series of predictive models using large regional cohorts of VLBW infants, followed by validation of the model in an independent group.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by Tufts New England Medical Center Evidence-base Practice Center (EPC), Boston, MA, under Contract No. 290-97-0019. It is expected to be available in the winter 2003. At that time, printed copies maybe obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 70, *Criteria for Determining Disability in Infants and Children: Low Birth Weight*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

www.ahrq.gov

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Evidence Report

Chapter 1. Introduction

The Social Security Administration (SSA) of the Department of Health and Human Services requested that the Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Center (EPC) program, produce an evidence report to determine whether specific factors or combination of factors alone or in addition to birth weight predict significant developmental disability in former premature infants and whether premature infants with such factors have long-term developmental disabilities. This is one of three reports requested by SSA in the broader topic of "Criteria for Determining Disability in Infants and Children." The evidence reports are prepared to assist the SSA in updating its *Listing of Impairments*, and revising its disability policy, as may be appropriate.

Definition of Disability

The definition of disability in children used for the purposes of this report came from the SSA and was based on a definition passed by Congress in 1996. Under Title XVI, a child under age 18 years will be considered disabled if he or she has a medically determinable physical or mental impairment or combination of impairments that causes marked and severe functional limitations, and that can be expected to cause death or that has lasted or can be expected to last for a continuous period of not less than 12 months.

Specific areas of functioning include: 1) acquiring and using information, 2) attending and completing tasks, 3) interacting and relating with others, 4) moving about and manipulating objects, 5) caring for yourself, 6) health and physical well-being. Disability is based on the degree to which the above functions are interfered with. Disability is established, if there are marked limitations in at least two areas or there is an extreme limitation in one area of functioning. Where standardized tests of function exist, the regulations define a "marked" degree of functional limitation as more than two but less than three standard deviations below the mean and an "extreme" limitation as three or more standard deviations below the mean. This definition is an administrative definition and is not always applicable to evidence available in the literature since disability as strictly and narrowly defined by US Congress and interpreted by the SSA is not the intent of the studies available in the literature. Although there is no single, standardized definition of disability, the literature provides overwhelming relevant evidence of functional impairments, disabilities, and limitations of VLBW.

Definition of Prematurity

Prematurity is defined both by gestational age and by birth weight criteria. The World Health Organization (WHO) defines prematurity as less than 37 weeks gestation. Birth weight has been and continues to be used as a surrogate definition of prematurity because birth weight and gestational age are closely correlated and birth weight data are readily available. Also, there is variable reliability of gestational age assessment in specific datasets. Defining specific gestational age or birth weight ranges often further refines the degree of prematurity.

The lower the gestational age, the more immature is an infant. Generally, the lower the birth weight, the more immature is an infant. However, birth weight is not a perfect measure of immaturity since infants may have birth weights that are disproportionate with their gestational age. For instance, some infants may be small or large for their gestational age.

Studies frequently focus on specific birth weight or gestational age groups. VLBW infants (birth weight less than 1500 grams) belong to one common birth weight category that targets infants at increased risk for problems associated with prematurity. This category of VLBW is often divided into subcategories of lower birth weights (less than 1250, less than 1000, less than 750 grams) to facilitate analyses of infants within different birth weight strata.

Similarly, gestational age categories of premature infants often include groupings of premature infants less than 28 weeks gestation, 28 to 32 weeks gestation, 32 to 36 weeks gestation, or less than 36 weeks gestation. Gestational age criteria, less than 32 weeks gestational age is considered by some authorities as "very premature" and less than 28 weeks gestational age as "extremely premature."

The Problem of Prematurity

Premature birth is an important public health problem due to the number of births in this category each year, the serious complications of prematurity, and the life-long tangible and intangible costs of caring for these infants. Among the 4,058,814 births in the USA in 2000, 58,124 (1.43%) were VLBW (less than or equal to 1500 grams) and 467,201 (11.6%) were born preterm as defined as less than 37 weeks gestational age (Table A).

Table A. Live birth distribution organized by birth weight and gestation in the United States in the year 2000 (National Vital Statistics Reports, 2000).

Birth weight grams	Number	Percent	Gestation weeks	Number	Percent
Total live births	4,058,814	100	Total live births	4,058,814	100
< 500 gm	5,952	0.15	<23 wk	9,243	0.2
500 – 750 gm	11,032	0.27	24-28 wk	19,652	0.5
751-1000 gm	11,878	0.29	28-31 wk	48,624	1.2
1001-1250 gm	13,291	0.33	32-35	218,928	5.5
1251-1500 gm	15,971	0.39	36-37	497,220	12.4
>1501 gm	3,995,849	98.57	38-47 wk	3,221,809	80.2
Not stated	4,841		Unknown	43,338	

Although VLBW is a relatively small proportion (1.4%) of total births in the US, this category of infants accounts for the highest neonatal mortality and morbidity among newborns, as well as significant tangible and intangible lifelong costs to the family and society for medical care, and ancillary health and educational services.

Advances in neonatal/perinatal medicine have improved the survival and the quality of survival of premature infants. Ninety-six percent of infants with birth weights between 1251 and 1500 grams survive in contrast to 77% of infants with birth weight less than 1250 grams (Stevenson, Wright, Lemons, et al., 1998). Despite these advances, infants born prematurely experience a disruption in the normal process of growth and development. The degree of disruption in the growth and development of each organ system, and the subsequent disabilities, are inversely proportional to gestational age at birth. For any adverse sequelae associated with premature birth, the incidence and the severity of the complication is inversely proportional to the gestational age [Table B]. For instance, 12% of infants with birth weight between 1251 grams and 1500 grams survived with at least one major, acute morbidity in contrast 53% with birth weight 501-1250 grams (Stevenson, Wright, Lemons, et al., 1998).

Table B: Mortality and morbidity of premature infants by birth weight born in NICHD Neonatal Research Network between January 1, 1993 and December 31, 1994 (Stevenson, Wright, Lemons, et al., 1998).

Complication	Birth Weight 501-1250 grams	Birth Weight 1251-1500 grams
N	3176	1417
Mortality (%)	23	4
Severe ICH* (Grade 3-4) (%)	16	3
Periventricular leukomalacia (%)	7	4
NCLD** at 36 wk PMA***	24	8
Necrotizing enterocolitis	9	3

* ICH = intracranial hemorrhage
** NCLD = neonatal chronic lung disease
*** PMA = postmenstrual age (gestational age + chronological age in weeks = adjusted gestational age)

Factors Associated with Disability in VLBW Infants

Surviving premature infants often sustain multi-organ system complications that may persist beyond the first few years of life and frequently result in permanent disabilities. Examples include major neurodevelopmental impairments, such as cerebral palsy (CP), mental retardation (MR), deafness and disorders of speech/language/communication, perception, attention, behavior and learning disorders, blindness or other visual disabilities, chronic lung disease, and growth retardation.

Complications of even a single organ system may have a profound impact upon other organ systems. A classic example of this is BPD, a neonatal chronic lung disease, which still occurs in 50% of extremely low birth weight (ELBW is defined as birth weight less than 1 kg) survivors (Stevenson, Wright, Lemons, et al., 1998). In addition to pulmonary disability, BPD predisposes infants to cardiovascular and neurodevelopmental disabilities, abnormal growth (height and weight), increased unfavorable ophthalmic risk, and more frequent infections (Farrell and Fiascone, 1997; Bancalari, 1997). Other determinants of disability of prematurity are summarized below. As previously noted, biomedical determinants of disability in premature infants are often compounded by determinants of social and psychological adaptation of these vulnerable children and their families.

CNS complications of prematurity, such as cerebral white matter damage, intraventricular hemorrhage, hypoxic-ischemic encephalopathy, and infection (e.g. meningoencephalitis), are related to both the degree of prematurity and illness acuity. CNS complications of prematurity are associated with life-long neurodevelopmental disabilities that may adversely impact an infant's cognitive, motor, visual, auditory, and psychosocial-behavioral development. Visual and audiologic compromises are individually important factors and have enormous impact on the overall cognitive, motor, and psychosocial development of premature babies (Hack and Fanaroff, 1999; Piesuch, Leonard, Cooper, et al., 1997; Kuban, Sanocka, Leviton, et al., 1999; Perlman, 1998; Stewart, Reynolds, Hope, et al., 1987; Stewart, Reynolds, Hope, et al., 1993). CNS complications of prematurity are associated with mental retardation and CP in premature infants.

ROP is an abnormal retinal vascular development. Severe ROP remains a leading cause of permanent vision compromise and blindness in premature infants (Murphy and Good, 1997; Oxford Registry of Vision Impairment, 1995). Although current retinal ablative therapy has helped reduce the incidence of retinal detachment and blindness, fewer than 20% of 5½-year-old children who developed threshold (severe) ROP and were treated achieved 20/40 vision (Cryotherapy for Retinopathy of Prematurity Group, 1996).

BPD is a chronic disease of the lung that affects almost exclusively premature infants. BPD is associated with increased mortality and morbidity both short-term and long-term. The multi-system morbidity of BPD may be associated with compromised cardiopulmonary function, growth, and neurosensory development.

Gastrointestinal complications (e.g. necrotizing enterocolitis and short-gut syndrome) (Stoll and Kliegman, 1994) and nutritional complications of prematurity (e.g. inadequate nutritional and nutrient intake related to prematurity, chronic hepatic injury secondary to prolonged total parenteral nutrition, and osteomalacia which compromises bone growth) may adversely impact life-long growth potential, and nutritional tolerance (Hay, Lucas, Heird, et al., 1999). Intrauterine circumstances and postnatal nutrition may program premature infants for life-long disorders (Lucas, 1990; Seckl, 1998).

The immune system of premature infants is also disrupted in its normal growth and development (Yoder and Polin, 1997). Premature infants are at increased risk for serious infections well beyond the neonatal hospitalization. The immune response to immunizations of infants who were born prematurely is less than that of infants who were born full term. The morbidity and mortality related to increased risk of infection among infants born prematurely may persist for years (Read, Clemens, and Klebanoff, 1994).

Inadequate growth in terms of both length and weight is a well-recognized, frequent, and persistent long-term complication of prematurity (Ehrenkranz, 2000; Doyle, 2000; Hack, 1996). Compromised growth among former premature infants may be due to multiple biomedical determinants including pulmonary, gastrointestinal, endocrine, neurological, and nutritional complications. Often the medical reasons for compromised growth in children born prematurely are compounded by familial, psychosocial, and socioeconomic factors, which independently compromise normal growth and development.

Educational achievement, self-esteem, psychosocial development, and effective integration into society are of particular concern as greater numbers of very premature infants are surviving in a society where resources for effective educational and psychosocial intervention are increasingly scarce and difficult to access. Former premature infants have increased incidence of learning disabilities and increased need for special education (Hack, Taylor, Klein, et al., 1994, Msall and Tremont, 2000). Obviously educational, emotional, and social successes, or the lack

thereof, for former premature infants have a major impact on how these individuals ultimately function as adults and upon the fabric of our society as a whole (Park and Hogan, 2000; Lester and Miller-Loncar, 2000; Saigal, 2000).

Thus numerous biomedical as well as familial, socioeconomic, and psychosocial factors related to prematurity predict disability in former premature infants. Unfortunately, many premature infants, especially the most immature infants, often experience a combination of factors, which further compound the magnitude and complexity of their life-long disabilities. Acute and long-term complications of premature infants, coupled with a family's ability to provide and advocate for their premature infants, have a substantial impact on the individual patient, their family, and society beyond the utilization of health care resources.

A systematic review of the incidence, types, and severity of factors, and the combination of factors, which predict long-term disabilities of premature infants, is worthwhile considering the societal impact of increasing number of surviving former premature infants. Review of recent literature may shed insights on whether factors related to premature birth predict future disability.

This review will summarize evidence on VLBW infants (i.e. prematurity) with or without other conditions to determine whether VLBW is associated with long-term disabling outcomes. The primary outcomes of interest included in this review are cerebral palsy, mental retardation, hearing/speech/language/and behavioral disability, visual disability, adverse pulmonary function, and disrupted growth.

Chapter 2. Methods

This evidence report is based on a systematic review of the literature. Our EPC formed an Evidence Review Team consisting of pediatricians and EPC methodological staff to review the literature and perform data abstraction and analysis. The Evidence Review Team held several meetings and teleconferences with external technical experts representing the Social Security Administration (SSA), the American Academy of Pediatrics, and the Disability Law Center to refine key questions proposed by the SSA, and identify issues central to this report. A comprehensive search of the medical literature was conducted to identify the evidence available to address the questions. For this evidence report, we compiled evidence tables of study features and results, appraised the methodological quality and applicability of the studies, assessed the correlations of the predictors and outcomes, and summarized the results.

From the outset, the external technical experts and members of the Evidence Review Team found it necessary to distinguish between two definitions of disability, one used by the SSA for administrative decision-making and the other found in the medical literature.

SSA's statutory definition of disability in children includes specific "medically determinable impairments" which result in "marked and severe functional limitations", coupled with a temporal dimension: the impairment and functional limitations can be expected to result in death, or have lasted or can be expected to last for a continuous period of not less that 12 months (SSA, 1999). The medical literature, however, defines impairment and disability more broadly. Moreover, very few studies have examined the association between VLBW and SSA-defined disability, per se. As a result, this report will use the terms disability and impairment as defined by study authors. The definitions reflect those endorsed by the World Health Organization (WHO). Impairment is any loss or abnormality of psychological, physiological or anatomical structure or function; disability is any restriction or lack of ability to perform an activity in a manner or within the range considered normal for a human being. This evidence report also uses the assessments of functional limitations as defined by study authors.

Key Questions Addressed by the Evidence Report

For infants with birth weight < 1200 grams and for infants with birth weights between 1200 grams and 1500 grams:

1. What factors or combination of factors alone or in addition to birth weight will predict significant developmental disability in former premature infants?

2. Are such infants developmentally disability at 1 year, 2 years, or beyond?

To identify the functional or physical outcomes related to disability and the elements believed to predict them, we sought evidence that a specific factor(s) was significantly associated with (i.e. demonstrates a relationship with) a specific disability. For example, very low birth weight infants with bronchopulmonary dysplasia have lower receptive language scores; the degree of immaturity influences the risk of CP and neurodevelopmental disability in VLBW infants. The EPC Evidence Review Team looked for evidence of association of VLBW with six outcome conditions: cerebral palsy (CP) and neurological impairments; abnormal cognitive

development and mental retardation; speech/language delay, hearing loss, behavioral disorders, and learning disabilities; visual impairment (with or without other conditions); pulmonary impairment (with or without other conditions); and growth impairment.

Literature Search Strategies

Disability is not a specific medical condition that can be readily searched for. Thus we had to look at many studies with related concepts (i.e., medically definable impairments that are related to disability) to identify potentially relevant studies. The Evidence Review Team identified a comprehensive list of predictors and outcomes by organ system vulnerable to VLBW (Table 4). The predictors and outcomes formed the basis of MESH search terms.

A systematic literature search was performed for full journal articles of original data. We did not include review articles, editorials, letters or abstracts. English language studies were identified primarily through Medline searches conducted between October 2000 and February 2001. We performed an updated search in September 2001 and again in January 2002. Supplemental searches were also performed in ERIC, PsycInfo, HealthStar and Embase. Additional studies were identified from reference lists, review and primary articles, and from domain experts and reviewers.

The Medline literature searches were conducted to identify clinical studies published from 1966 through the search dates. Development of the search strategies was an iterative process that included input from domain experts. Each search strategy was designed to yield approximately 10,000 titles and the preliminary searches yielded multiple tens of thousands of titles. Samples of these searches were screened and keywords from potentially relevant articles were then used to refine future searches. All searches were limited to studies of humans that were published in English and included children (age < 18 years). Details of the literature searches are presented in Table 4 in Appendix A.

Search Results

The initial search for the literature review consisted of: 1) Medline search from 1966 through November 2001 (2,885 abstracts), 2) HealthStar search from 1975 to October 2000 (26 abstracts), 3) PsycInfo search from 1984 to September 2000 (333 abstracts), 4) ERIC search from 1966 to August 2000 (140). The total number of abstracts in the primary search was 3,384.

These initial search strategies used the text words “low birth weight”, “preterm infant or newborn”, “disability”, “limitation”, “handicap”, “impairment”, “follow-up studies”, “longitudinal studies”, “cohort studies”, “case-control”, “randomized controlled trials”, “research design”, etc. The search strategies were updated in January 2001, using as MESH terms the list of predictors and outcomes by organ system vulnerable to VLBW. A secondary search in January 2002 for the year cohort 1985 through 2001, used MESH headings “Population: infant, premature” or “infant, low birth weight”; Study design: “follow-up” or “cohort”; Disease: predictor and outcome terms such as cerebral palsy, retinopathy of prematurity, etc.

Using such a very broad search strategy, the EPC identified 13,130 articles. The study designs included were cohort studies, case-control studies, and randomized controlled trials, which compared VLBW outcomes to normal birth weight outcomes.

Limitations of the Literature Search

The literature search protocols and study inclusion criteria were both designed to identify all possible correlations available in the literature. However, while literature searches were intended to be comprehensive, they may not have been exhaustive. As noted above, search strategies were limited to focus on studies likely to be relevant. Searches were limited to English language publications. Hand searches of journal were not performed, and review articles and textbook chapters were not systematically searched. Nonetheless, important studies known to the domain experts and studies found in reference lists were included in the review.

Study Selection

Results from Abstract Screening

By the second literature search in January of 2001, a total of 16,614 abstracts had been identified from four databases. We screened 16,164 abstracts that covered 13 categories: central nervous system (2,930); ophthalmology (398); audiology (80), pulmonary (1,833); nutrition and growth (2,533); medication (dexamethasome) (183); perinatal factors (875); illness acuity (56); infectious diseases (2,378); gastrointestinal (477); bone/osteomalacia (10); health care (466); and immune disorder (921). Approximately 1,693 articles were retrieved after screening of the abstracts.

Because we used search strategies with high sensitivity but low specificity to avoid missing potential relevant articles for this evidence report, the result was a large number of abstracts requiring review. Physician members of the Evidence Review Team screened each article against the inclusion criteria.

We focused the literature review primarily on premature infants born weighing less than 1,500 grams, including all subcategories of birth weights (e.g. less than 1,250 grams, less than 1,000 grams, and less than 750 grams). We also incorporated literature that included infants with birth weight less than 1,500 grams within a larger premature cohort and literature on infants whose prematurity was defined by gestational age, since many studies use gestational age and not birth weight criteria.

The Evidence Review Team reviewed all studies (retrospective or prospective) reporting impairments in infants or children who weighed 2000 grams or less, whose gestational age was 35 week or less, or whose birth weight or gestational age were below these thresholds. Longitudinal data for minimum of 6 months was preferred. Table C lists the inclusion and exclusion criteria.

Table C. Inclusion/exclusion criteria

Include	
Randomized controlled trials, case control studies, prospective cohort or retrospective cohort studies	• Only abstract data from primary studies • English language • Population (BW <= 2000gm and GA < 35 wk) • At least 10 subjects • At least one of the listed predictors (See Table 4) • At least one of the listed outcomes (See Table 4)
Exclude	• Articles if infants born before 1980 • Articles published before 1985

Revised Study Selection Criteria

The EPC categorized by sample size and birth year the articles that met the minimum inclusion criteria for LBW: articles with one or more relevant clinical outcomes; follow-up duration greater than of equal to 6 months; enrolled patients born after 1980, and study size greater than 10.

We then established a hierarchy of studies based on study size and birth year of the infants. Studies with birth years from 1990 onward were given preference, followed by studies with birth years between 1985 to 1989 and then studies before 1985. Within each birth year cohort, studies with more than 100 infants were selected first, followed by studies with 50 to 100 infants and less than 50 infants. Using this classification hierarchy, we worked through the most relevant (recent) and strongest (largest study size) studies in succession before older and smaller studies, until a complement of 178 articles was achieved.

Outcomes and Predictors Considered in this Evidence Report

The Evidence Review Team identified a list of predictors and outcomes (Table D). The universe of outcomes included those, which SSA recognizes as medically determinable physical or mental impairments that result from anatomical, physiological, or psychological abnormalities (SSA, 1999).

Table D. List of predictors and outcomes

PREDICTORS	OUTCOMES
Various BW categories (such as…	**All outcomes listed below:**
< 1500 gm	Neurodevelopmental/behavioral outcomes,
< 1250 gm	Vision, Hearing, Pulmonary, Growth, etc.
< 1 kg	
< 750 gm	
Various Gestational Age categories (such as	**All outcomes listed below**:
< 35 weeks	Neurodevelopmental/behavioral outcomes,
<32 weeks	Vision, Hearing, Pulmonary, Growth, etc.
<30 weeks	
<28 weeks	
<26 weeks	
Central Nervous System – CNS	
Intracranial /intraventricular hemorrhage	Motor delay/ Cerebral palsy
Periventricular leukomalacia	Cognitive delay Mental retardation
Seizures	Behavioral
Hypoxic-Ischemic encephalopathy (HIE)	School performance
Ventriculomegaly/ ventricular dilatation	Learning disabilities
Primary Outcomes feeding / swallowing	
Prolonged apnea	Hearing disorders /Deafness
Intrauterine substance abuse (opiates, cocaine, ethanol)	Visual impairment/Blindness
Low Apgar Score	Speech / Language / Communication disorder
	Feeding / Swallowing disorders
	Post hemorrhagic hydrocephalus (PHH)
	Ventricular peritoneal (VP) shunt & other disabilities
	Neurodevelopmental Impression: Normal, Abnormal, Suspect
	Neurological examination: Normal, Abnormal, Suspect
Ophthalmology	
ROP (retinopathy of prematurity)	Visual outcome
HIE	
Audiology	
Aminoglycosides	Hearing outcomes
Furosemide	
Hearing Screen Failure	
Cardiovascular diseases	
Cor pulmonale	
Pulmonary	
Chronic Lung Disease	Asthma
Bronchopulmonary dysplasia	Pulmonary function
	Tracheostomy
	Upper airway
	Chronic Lung Disease
	Reactive airway
	Exercise tolerance

PREDICTORS	OUTCOMES
Gastrointestinal	
Short gut	Short gut
Necrotizing “enterocolitis” – NEC	Cholestasis / Cirrhosis
Total parenteral nutrition – TPN	Gastrostomies / GERD / Fundoplication
Cholestasis	
Nutrition / Growth	
	Weight
	Height
Bone	
Osteomalacia	Osteomalacia
Infectious Diseases	
RSV	
Meningitis	
Sepsis	
Congenital/Acquired Immune Disorders	
Hospital / Health Care Resource Utilization	
	Rehospitalization (for any reason)
	Costs
	Physical/occupational therapy
	Orthopedic
Illness Acuity	
SNAP	
CRIB	
Medications	
Dexamethasone	
Perinatal factors	
Drug hx	
Antenatal steroid use	
Chorioamnionitis	
Chorionic villous sampling	
Diabetes	
Pre-eclampsia	

Data Abstraction Process

EPC staff developed draft data abstraction forms, which were refined through an iterative process with the methodologic and domain expert members of the Evidence Review Team (Appendix B). Information abstracted for assessment included the study population characteristics (i.e. such information as age, height, weight and gestational age), inclusion and exclusion information, study design, study funding source, the results and conclusions of the

study. In addition, data for quality assessment of individual studies were systematically abstracted, including data for rating the internal validity and applicability of the study.

Pediatrician domain experts performed all the data abstraction. The EPC staff trained abstractors. As part of the training each Team Member abstracted three studies in duplicate with the Team Leader and meetings were held to discuss discrepancies. After training, all remaining studies were abstracted by one pediatrician. Abstracted data were verified by a member of the EPC staff when the data was transferred to evidence and summary tables.

Reporting the Evidence

We summarized the evidence we found for the LBW condition in two complementary forms. The evidence tables contain detailed information about the study characteristics, population and disease characteristics, patient demographics, treatment comparisons, and outcome measures. We used this information to derive an evidence-grade to provide an indication of "quality" for each of the studies used to address the key questions. This evidence-grading scheme captures dimensions of a study that are important for the proper interpretation of the evidence: internal validity, applicability, magnitude of treatment effect (for treatment studies), and the size of the study. This evidence-grading scheme is used as part of the reporting of the results.

A narrative and a tabular summary of the strength and quality of the evidence of each study are provided for each outcome condition. For some conditions, studies are grouped first by study sample disease type. For some conditions, studies are ordered first by methodological quality (best to worst), then by study size (largest to smallest). For other conditions, studies are grouped first by methodological quality, then by applicability of study sample.

Evidence Tables

EPC staff constructed evidence tables for each the outcomes within the six conditions of interest. These tables are presented in Chapter 7 of this evidence report:

Table E. Evidence tables created in this report

Table number	Table name
Evidence Table 1	Studies evaluating association of LBW and multiple outcomes: CNS, Eye, Lung, Growth, etc
Evidence Table 2	Randomized Control Trials for LBW infants and multiple outcomes: CNS, Eye, Lung, Growth, etc
Evidence Table 3	Studies evaluating association of LBW and cerebral palsy and neurological outcomes
Evidence Table 4	Studies evaluating treatment effects of LBW and cerebral palsy and neurological outcomes

Table number	Table name
Evidence Table 5A, B	Studies evaluating association of LBW with speech/language and hearing loss
Evidence Table 6A, B	Studies evaluating association of LBW with behavioral disorders and school performance
Evidence Table 7	Studies of association of LBW to ophthalmic outcomes
Evidence Table 8	Studies of treatment effects for LBW infants with retinopathy of prematurity (ROP)
Evidence Table 9	Studies evaluating association of LBW and pulmonary outcomes
Evidence Table 10	Studies evaluating association of LBW and bone and growth outcomes
Evidence Table 11	Randomized Controlled Trials in LBW Neonates for growth outcomes
Evidence Table 12	Studies evaluating association of LBW and nutritional outcomes
Evidence Table 13	Studies evaluating association of LBW and other outcomes

Summarizing the Evidence of Individual Studies

Grading of evidence can be useful in appreciating the overall "quality" of a group of studies addressing a question. Over two-dozen scales have been proposed to evaluate the quality of randomized controlled trials (Moher, Jadad, Nichol, et al., 1995). While it may be desirable to have a simple evidence grading system using a single quantity, the "quality" of evidence is multi-dimensional and a single metric cannot fully capture information needed to interpret a clinical study (Ioannidis and Lau, 1998). A recent empirical study applied 25 quality scales to one meta-analysis and found that different quality scales could result in different conclusions hence quality scales are inconsistent among themselves (Juni, Witschi, Bloch, et al., 1999). Another empirical study demonstrated the greater usefulness of assessing studies according to specific study design features (Lijmer, Mol, Heisterkamp, et al., 1999).

Methodological Quality

Methodological quality, often referred to as internal validity, addresses the design, conduct, and reporting of the clinical trial. Some of the items belonging to this entity have been widely used in various "quality" scales and usually include items such as concealment of random allocation, treatment blinding, and handling of dropouts. In this evidence report, we define a three category internal validity scale: A (least bias), B (susceptible to some bias), C (likely to have large bias).

Study Quality

A **Least bias**. Prospective study that is clearly reported, uses explicit and appropriate eligibility criteria, uses appropriate definitions of predictors and outcomes that are properly measured or estimated, uses appropriate statistical and analytical methods, and is free of obvious bias. Retrospective studies, irrespective of other aspects of quality, cannot be in category A. Study size should not be a factor for quality.

B **Susceptible to some bias**. Prospective or retrospective study that does not meet qualifications of category A but deficiencies are unlikely to cause major bias.

C **Likely to have a large bias**. Major deficiencies that cannot exclude possibility of significant bias. Insufficiently reported information.

Applicability

Applicability, also known as generalizability or external validity, addresses the issue of whether the evidence from the study population is sufficiently broad as to be able to generalize to the population at large. Individual studies are often unable to achieve broad applicability due to restricted study population characteristics and a small number of study subjects (Lau, Ioannidis, Schmid, 1997).

For questions where all studies within a given table evaluate children with the same (or similar) diseases, a designation for applicability was assigned to each article, according to the following three-level scale:

Sample is representative of the whole population of babies with prematurity and low birth weight condition relevant to the topic question (eg, whole population of preterm babies and infants with BW 1200-2000g). This implies a reasonable sample size, a diverse group of infants with the condition, and inclusion/exclusion criteria that will capture the whole group.

A relevant sub-group or subgroups of very low birth weight and prematurity, (only those with a specific, though common, condition eg: BW 1200-1500 grams).

A very narrow group of subjects who are a limited sample of very low birth weight and prematurity (only those with a relatively rare condition, or a non-representative demographic group e.g. crack babies).

Study Size

The study (sample) size is used as a measure of the weight of the evidence. In general, large studies provide more precise estimates of prevalence and associations. In addition, large studies are more likely to have wide applicability, depending on eligibility criteria. However, large study size does not guarantee applicability.

Results

The type of results available is determined by each study's design, the purpose of the study, and the question(s) being asked. Therefore, the results presented vary across summary tables. Summary tables for some question present either association or percentage of subjects with impairment. Other questions include separate columns for the strength of the association of the predictors with the outcome of interest. For appropriate topics, associations are described with the following arrows:

- ⬆ Statistically significant positive association found between the predictor and the outcome. Significantly increased the risk of MR/CP/Growth/BPD/POP (any disability) associated with VLBW or GA.

- ⬇ Statistically significant negative association found. Significantly decreased the risk of MR/CP/Growth/BPD/POP (any disability) associated with VLBW or GA.

- ⇔ No association.

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
	66	BW <1501 g GA: ND	Clinical	20%		B
Sethi, 1996 96334245 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	17	BW: 1197 (625-1500)GA: 30 (27-36)	Spastic CP, diagnosed by "complete neuro exams"	41%		C
Cooke, 1999 993806719	1187	ND	Data from Regional Cerebral Palsy Rgst	10%		C
Dammann, 2001 21221175	324	BW: ND GA: ND	ND	10%		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		Applica-bility	Quality
					Univariate	Multivariate		
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		Applica-bility	Quality
				Univariate	Multivariate		
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 Doyle and Victorian Infant Collaborative Study Group, 2001 11433066	212	1985-1987	BW: 500-999 GA: ND	DQ < -3 SD DQ –3 to –2 SD	6% 4%		B
	241	1991-1992	BW: 500-999 GA: ND	DQ < -3 SD DQ –3 to –2 SD	6% 5%		
Battin, 1998 99002694	44	1991-1993	BW: < 800 GA: 23-25	Sig. impairment Multi. Handicaps	36% 14%		C

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	Indomethacin: BW: 945 GA: 28 Placebo: BW: 988 GA: 28	Low dose indomethacin decreased both incidence and severity of IVH	IQ < 70	↓		A
Schmidt, 2001 21298249	1202	Indomethacin: BW: 782 GA: 26 Placebo: 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	<u>VLBW grp</u>: BW: 1088 GA: 28 <u>LBW: grp</u>: 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 $\geq$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 $\geq$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 Sprachentwicklungstest 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 $<10^{th}$ 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	Qualit y
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 Cryotherapy: 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	Association	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	Association	Applicability	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	⇔	🚹🚹	B
				HC	⬇		
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 $<3^{rd}$ and $<10^{th}$ 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 Re-hospitalization for poor growth Re-hospitalization for poor FTT	⇔ ↑ ↑		B

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 neurodevelopment 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(<10 % 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 10^{th} percentile at 1 year of life. However, by two years of life, less than 35% of subjects had weights less than the 10^{th} 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

Chapter 4. Conclusions

Overall

We reviewed a large multiple of citations (>16,000) and included data from 170 articles in the analysis. Among the final articles abstracted for this review, the quality and methodology were variable, as expected, because we incorporated various study designs to address the key questions. Many of the final articles selected were of good to excellent quality. The study question "VLBW with or without other conditions was associated with disability" was a relevant and important question. However, the original intent of the majority (if not all) of the studies that evaluated the association of prematurity or conditions of prematurity with disability did not specifically address this question in this manner. Disability as defined by the U.S. Congress and interpreted by SSA was not the original intent of the studies reviewed. Despite these issues, the evidence of the articles reviewed overwhelmingly support the fact that VLBW with or without specific conditions was associated with increased risk of long-term disabilities. All of the articles reviewed evaluated disabling outcomes that occur ≥12 months of age and were likely to remain disabling ≥1 year. Unfortunately, most of the impairments were lifelong. The evidence to support the association of VLBW with specific outcomes is noted below.

Neurodevelopmental Disabilities

The evidence identified by our search methods clearly demonstrates that VLBW infants have high rates of neurodevelopmental disabilities, including cognitive (MR), neuromotor (CP), neurosensory (visual and auditory) impairments, and communication (language/speech)/ behavioral disorders compared with normal birth weight controls. The review also found evidence that VLBW infants have increased risk of long-term, clinically significant compromise in growth compared with normal birth weight controls. The evidence illustrates that VLBW infants with BPD have increased risk of significant pulmonary impairment that imposes a respiratory disability for variable lengths of time, especially in children who sustained severe BPD during their early neonatal course. The prevalence and severity of all these disabilities is even higher among ELBW infants.

Co-morbidities of prematurity, such as CNS injury, ROP, auditory/communication disorder, BPD, and feeding problems, individually and collectively play significant roles in subsequent, long-term disabilities. The co-existence of these morbidities is precisely the reason VLBW children have multiple handicaps. But even the presence of one handicap, e.g. visual disability, and/or hearing loss, greatly influences other realms of development and growth, and may lead to additional disabilities in speech and language, behavior problems and learning that affect school performance and limit daily function.

Methodologically sound studies demonstrate that a greater proportion of VLBW and ELBW infants have multiple health problems and increased utilization of health care resources compared to full-term controls. These disabilities result in significant tangible and intangible costs to the individual child, its family, and society.

Robust, well designed, and carefully validated predictive models for MR and CP in VLBW infants, constructed with clinical information available at the time of hospital discharge do not yet exist. The ability to accurately predict neurodevelopmental outcome in the individual neonate on the basis of identifiable risk factors has had limited success. However, large and methodologically sound studies performed in a variety of settings have identified several risk factors that appear to have consistent and independent associations with subsequent abnormal cognitive and neuromotor development. In particular, cerebral white matter damage in the form of cystic PVL, severe (grade III or IV) IVH, and ventriculomegaly are the strongest indicators of risk for CP, neuromotor abnormalities, and MR. Timing of cranial ultrasonography is also critical to maximizing detection of the strongest risk factors. The 40-week adjusted gestational age cranial ultrasound had the highest odds ratio for predicting CP.

Increasing evidence indicates that antenatal events contribute to the etiology and sequence of events leading to neurologic impairment, CP, and MR in VLBW infants. Antenatal inflammation, chorioamnionitis, and fetal hypoxia/acidosis may play important roles by stimulating a fetal inflammatory response that injures the immature cerebral white matter. Other antenatal events such as premature rupture of membranes (which may be related to antenatal inflammation and subclinical infection) and abruption have been identified as antenatal risk factors contributing to an increased risk of CP and/or neurodevelopmental disability in premature infants. The degree of prematurity and CNS injury in conjunction with these antenatal factors appear to influence the development of neurologic disability, including CP and MR.

Many studies strongly implicate BPD as an important contributor to subnormal cognitive and motor performance. BPD frequently co-exists with other disabling conditions commonly seen in VLBW/ ELBW infants, such as cerebral white matter damage and IVH, which impact cognitive and motor outcome. Our methods identified many studies documenting a significant independent relationship between bronchopulmonary dysplasia (BPD) and abnormal cognitive development in both VLBW and ELBW infants. Increasingly, evidence supports the association of postnatal administration of corticosteroids (specifically dexamethasone) for the amelioration or prevention of BPD as a contributor, independent of BPD, to developmental delay and CP.

The relationship between biological/medical risk factors and social/parenting 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. Although biomedical risk factors, such as PVL and ROP, are important determinants of subsequent disability in VLBW infants, it is also clear that social/parenting risk factors are critical, independent influences on the outcome of high-risk VLBW children. Neurologic and cognitive abnormalities are higher in infants with adverse parenting factors (e.g. abuse and/or neglect). The evidence illustrates the vulnerability of high-medical risk VLBW infants to parenting, social, and environmental risk factors. It also 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.

Other risk factors that appear to have associations with cognitive development include race, gender, socioeconomic status as indicated by markers such as mother's level of education, and illness severity as measured by objective scoring systems. The presence of deficits on physical, neurological, visual, auditory, and developmental examinations at 6 or 12 months may significantly refine assessment of risk for sustained neurodevelopmental abnormality. Knowledge of these risk factors encourages the attempt to develop a predictive model(s) using a large cohort of VLBW infants, followed by validation of the model in an independent group.

Speech and Language

Strong evidence indicates increased risk of speech and language delays in VLBW infants. Factors associated with increasing this incidence include patent ductus arteriosus and intracranial ultrasound findings of cerebral white matter damage and IVH, as well as combined neonatal factors of duration of mechanical ventilation, acidosis, seizures, infection and hypoglycemia.

The data on the incidence of hearing loss in ELBW infants are conflicting: four studies report higher incidence ranging 9 to 14% and nine studies report low incidence or rates similar to their full-term controls. This discrepancy may be due to variations in testing methods used, which were frequently not reported in the studies reviewed. Infants with hearing loss are more likely to have had a high illness acuity in their neonatal course with combined exposures to severe hyperbilirubinemia and acidosis, hyperbilirubinemia and aminoglycoside use, elevated creatinine and furosemide use, and aminoglycoside and furosemide use.

The evidence is strong that VLBW infants have increased attention problems and more passive temperament. Intracranial lesions, CP, impaired cognition, and urban socioeconomic setting was associated with the increased incidence.

Available evidence suggests that VLBW infants are at higher risk for learning disabilities and future difficulties in school. Predictors of these problems in VLBW infants include small head circumference and decreased head growth velocity during the first several months of life.

Visual Disability

VLBW infants also are at increased risk for retinal and non-retinal ophthalmic disorders that lead to visual disability. This increased risk is primarily due to complications of prematurity, primarily ROP and CNS injury. The more immature the infant, the greater is its risk for any, as well as for severe ROP and CNS injury. The greater the severity of ROP, the greater is the risk for unfavorable structural and functional outcome (reduced acuity, blindness, abnormal fixation, strabismus, myopia, amblyopia). Infants with threshold (severe) ROP are known to be at very high risk for unfavorable structural and functional ophthalmic outcome. Treatment options for severe ROP, such as retinal ablation with laser therapy, are beneficial, but not always successful. Even when treatment is successful, the long-term visual outcome of infants with severe ROP is not satisfactory. Among threshold ROP eyes that are treated, 40 to 60% of the eyes have unfavorable visual outcome and 20 to 30% of the eyes become blind.

CNS injury is a separate, independent contributor to visual disability that often co-exists with ROP in the premature VLBW infant. The more severe the cerebral white matter damage, as demonstrated by cystic PVL, ventriculomegaly, and IVH, the greater the risk of cortical visual disability. The degree of visual impairment correlates very strongly with the degree of neurodevelopmental impairment. This evidence emphasizes the importance of ocular assessment of VLBW children with CNS damage, and neurodevelopmental assessment in VLBW children with visual disabilities.

The most common visual disabilities in VLBW infants resulting from ROP and/or CNS injury include significant reduction in visual acuity (including blindness), abnormal fixation, strabismus, and severe myopia. Visual fields, contrast sensitivity, and other visual functions may also be impaired. BPD also appears to contribute to greater visual impairment. Thus, ROP, CNS

injury, and BPD individually and collectively contribute to visual disability in the premature VLBW infant.

The first year of life is a critical period for visual development, and vision is a crucial determinant of early motor and cognitive development. Careful assessment of vision in visually high-risk infants is essential during the neonatal and infancy period, and must continue through the first several months and years of life to permit detection of abnormal acuity, strabismus, amblyopia, refractive errors, etc. Studies emphasize that premature infants at risk for ophthalmic disability, and those with documented ophthalmic sequelae early in infancy, require close, long-term follow-up due to evidence that infants may have progressive, ophthalmic deterioration over time. Omission of or inadequate follow-up may contribute to worsening visual outcome or blindness if appropriate timing of interventions for treatable conditions is missed.

No single visual test at one point in time can adequately assess the various multiple visual functions. Meaningful evaluation of visual function requires comprehensive, repeated, long-term assessments for acuity, refractive error, ocular motility, fixation, visual fields, contrast sensitivity, and color vision in conjunction with neurodevelopmental assessment. The specific method and timing of the ocular tests must be in accordance with the infant's age and capabilities. The reality of life-long therapeutic, educational, psychosocial, and socioeconomic significance and costs of visually disabled VLBW children highlights the importance of ocular assessment and appropriate timing of intervention. This, in turn, helps to minimize visual disability and to maximize the adaptation if visual disability exists.

Pulmonary Disability

The studies reviewed indicate that VLBW infants with BPD are at increased risk for long-term pulmonary disability. The greater the severity of BPD, the greater is the association with long-term pulmonary impairment and need for re-hospitalization. On the whole, VLBW preterm infants without BPD are comparable to full-term children in terms of pulmonary outcome. VLBW infants with less severe BPD may have respiratory disability primarily during the first two years of life. VLBW infants with more severe BPD may have persistent lung disease during young childhood and continuing through to their adolescent, young adult years.

Preterm children with chronic lung disease due to BPD vary in their manifestations of pulmonary disability. Lung dysfunction can be demonstrated by formal pulmonary function testing and abnormal physical examination findings. The most frequently described consequences of pulmonary disability are increased respiratory symptoms (e.g. wheezing and cough), respiratory illnesses, and the need for respiratory medications. All of these reflect the underlying physiologic consequences of aberrant growth, development and function of injured premature lungs. Re-admission to the hospital for respiratory illnesses, such as asthma, pneumonia, recurrent bronchitis, and exacerbations of chronic lung disease, is unfortunately common in the first two years of life. The need for hospital admission for issues related to failure- to-thrive due to poor growth, surgeries or other reasons is also increased in VLBW infants with BPD compared to full term infants. Although it appears that premature infants in the current era of neonatal care do not have as severe BPD as in the era prior to the widespread use of antenatal steroids and surfactant, BPD still accounts for significant long-term, multi-system morbidity.

Poor Growth

Recent studies continue to provide evidence that VLBW infants have significantly lower weight and height, and may have abnormal body composition and bone mineralization, during the first years of life compared to children who were born full-term. Growth impairment in VLBW/ELBW infants is due largely to prolonged, acute neonatal illnesses and subsequent chronic illnesses (e.g. BPD, gastroesophageal reflux, short-gut syndrome). But failure to grow (i.e. weight $<3^{rd}$ and $<10^{th}$ percentile through 2 years of age) in high risk VLBW/ELBW infants is also strongly associated with neurosensory developmental abnormalities and motor skills that impact the child's feeding ability. Attainment of appropriate growth and nutrition in VLBW infants is an important challenge that requires conscientious attention over the course of months and years after initial discharge from the neonatal unit. This is particularly true for children who have long-term disabilities related to BPD, short-gut syndrome from necrotizing enterocolitis, and neuromotor, neurosensory, cognitive, and/or neurobehavioral disorders within the context of an adverse social/parenting setting.

Chapter 5. Future Research

In this section, we propose two prospective health service research opportunities. These proposals would help SSA evaluate the application process of VLBW disability criteria and determine the appropriateness of the criteria for identifying high-risk VLBW infants. In addition, we propose concepts to improve identification of risk factors and outcomes.

Evaluation of the Application Process of SSA VLBW Disability Criteria

This proposed research concept involves more complete reporting of regional applications of the VLBW disability criteria based on the entire VLBW population within regions. The proposed research would document baseline risk factor data on all VLBW infants born within participating regions, follow surviving VLBW infants for specified periods of time with respect to pre-specified, disabilities (1, 2, 3, 5, 10, 12 years of age), and document the proportion of VLBW who come to the attention of SSA, relative to the entire regional cohort of VLBW infants. This research proposal would accomplish several objectives:

- SSA could compare baseline characteristics of VLBW infants who do and do not come to the attention of SSA.

- SSA could assess the consistency of applying SSA VLBW Disability Criteria. This would, in turn, provide greater insight into reasons for successful programmatic implementation and impediments of applying the criteria. It would provide insight regarding the effectiveness of identifying high-risk VLBW infants.

- Provide an opportunity for SSA to standardize uniformity in assessing disabilities in this high-risk cohort at different ages.

- Identify barriers to referring infants to SSA.

Determine the Appropriateness of the New VLBW Disability Criteria Proposed by SSA Based on the Evidence of This Report.

This proposed research concept involves the evaluation of VLBW infants who do and do not meet the new disability criteria to ascertain the sensitivity, specificity, positive and negative predictive values of the new SSA disability criteria for VLBW infants. This second proposed research concept is a natural “next- step” linked to the first research concept proposed above. The combination of these two concepts affords the SSA the ability to know if the process and the criteria are achieving the objectives established by the SSA.

Proposal to Improve the Evidence of Predictors and Predictive Models

Improve Definitions of Predictors

The current literature provides evidence, which confirms that VLBW infants with or without various conditions are at increased risk for multiple long-term disabilities. Large and methodologically sound studies performed in a variety of settings have identified several risk factors (e.g. gestational age, CNS damage, ROP, BPD) that appear to have consistent and independent associations with subsequent abnormal neurodevelopmental outcome. The identified demographic and clinical factors are important, helpful, and necessary evidence, but current definitions of clinical risk factors have limitations. Each risk factor has a spectrum of severity. Three examples for possible definition refinement include 1) criteria for screening and diagnosis of cerebral WMD, 2) criteria for high-risk ROP, and 3) criteria for high-risk BPD. More specific definition of the predictors may better characterize an infant's risk for having a specific disability(ies).

In addition to refining predictor definitions, the development of a robust, well designed, and carefully validated predictive model, constructed with clinically significant factors available at the time of hospital discharge, could create a "profile" of a VLBW infant at risk for specific disabilities. Such a predictive model does not yet exist. A series of models could be developed and validated to incorporate new factors and information noted during the specified times of follow-up. The presence or absence of deficits on physical, neurological, and developmental examinations at subsequent follow-up appointments (e.g. at 6, 12, 24 months of corrected age) may significantly refine assessment of risk for sustained disabilities. Refinement of risk factors invites a systematic, collaborative effort to develop a series of predictive models using large regional cohorts of VLBW infants, followed by validation of the model in an independent group.

Identify New Predictors

Current predictors of disabilities in VLBW infants are markers of the underlying complications and morbidities. Multiple levels of risk factors exist, including demographic and clinical factors, as well as physiologic, biochemical, molecular, and genetic factors. Most of the factors beyond demographic and clinical data are not well described. Better understanding of pathogenesis and the "biochemical, molecular, and genetic" epidemiology of a disease process could provide a more comprehensive profile of the "condition(s)" that predispose to VLBW infants to certain disabilities. Current research is underway to refine our molecular and clinical understanding of the determinants of major morbidities (CNS damage, ROP, BPD) of extremely low gestational age neonates. These and other studies should refine our ability to improve criteria for infants at risk for adverse outcomes.

Feasibility of Future Research Proposals

These proposals are ambitious. The logistical issues of organizing, funding, and implementing these long-term collaborative endeavors present enormous, but achievable, challenges. The fact that large scale follow-up of VLBW infants over many years can be accomplished is reflected in the studies reviewed. Regions that have committed leadership and established neonatal programs for achieving the objectives noted above should be solicited in order to ensure the success of this endeavor.

The follow-up of VLBW infants is a major public health concern. Prospective neonatal health services research that facilitates linkage of significant risk factors with outcomes is essential to care providers in assessing care practices and to agencies providing health services. Research efforts to identify amenable determinants of premature birth, CNS damage, ROP, and BPD are in progress. Research promoting the identification and dissemination of "best care practices", as well as determinants of prematurity and its consequences should be encouraged and supported.

The VLBW child with long-term disabilities is a challenge to his/her family, teachers, physicians, and society. This challenge often stems from the complexities of the child's issues coupled with inadequate resources and support for effective assessment and intervention on a long-term basis. The standard techniques currently available to evaluate function are often not adequate to describe the extent and nature of impairment. Educational interventions will vary for children with different disabilities. Although specific educational programs exist for children with disabilities, they may not be widely accessible. The potential for a child with multiple handicaps to live independently and productively is often compromised if access to effective rehabilitation is not available or limited. For prematurely born children who sustain complications that result in neurodevelopmental and neurosensory disability, effective efforts must be made to identify these children and their specific issues/needs early in infancy. These children need recurrent reassessment of their abilities and/or disabilities over time in order to detect progression of disabilities and to provide appropriate early intervention or rehabilitation to maximize their capabilities and limit their disabilities.

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Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Akerman 1992 93255928	Location: Sweden Years of Birth: ND Median GA (range), wk: 7 pairs < 37 wks Median BW (range), g: 37 < 2500 g (23 of these > 37 wks) Male: 46% Race: ND Enrolled: 35 parents who were expecting twins Evaluated: 68 (34 twin pairs) Number of sites: 1	ND (35 parents who were expecting twins)	ND (One child in a twin pair was stillborn)	Low born twins (68, or 34 pairs)	Prospective longitudinal cohort (at 9, 18 months, and 4 years)
Thompson 1993 93234177	Location: South African Years of Birth: 1988 to 1989 Mean GA (range), wk: 32±2.5 (26.8-40) Mean BW (range), g: 1044±149 (600-1250) Male: 50% Race: ND Enrolled: 143 Evaluated: 143 Number of sites: 1	BW <1250 g ventilated infants Survived to hospital discharge	Infants <900g and <28week are not routinely ventilated	VLBW ventilated infants (143)	Prospective cohort (2 years)
Rademaker 1994 95003452	Location: Netherlands Years of Birth: 9/1989-9/1992 Mean GA (range), wk: 25-32 Mean BW (range), g: 820-2200 Male: 70% Race: ND Enrolled: 20 Evaluated: 20 Number of sites: 1	GA = 32 weeks Unilateral parenchymal involvement on cranial ultrasound associated with GLH Germinal layer hemorrhage or IVH	ND	Preterm infants (GA 32 weeks or less) with diagnosis of unilateral parenchymal involvement (20)	Prospective cohort

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Vonderveid 1994 94297368	Location: Italy Years of Birth: 1987-1988 Mean GA: ND Mean BW : ND (only range: 500-1499 g) Male: ND Race: ND Enrolled: 634 Evaluated: 390 (alive at 2 yrs) Number of sites: 8	All newborns with BW: 500-1500 g BW Admitted in one of the 8 participating NICUs Born between 1/1987-12/1988	ND	Sample 1: VLBW (500-1000 g): (191) Sample 2: LBW (1000-1499f): (443)	Prospective cohort study (24 mo CA)

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Kraybill 1995 95264242	Location: USA Years of Birth: 1986-1989 **Sample with F/up at 1 year** Mean GA: Sample 1: 28.2 ±1.9 Sample 2: 28.1 ±2.0 Mean BW: Sample 1: 1022 ±177 Sample 2: 1028 ±184 Male: Sample 1: 51% Sample 2: 52% Race: Sample 1: White: 21%, Black: 53%, Hispanic: 23%, Other; 4% Sample 2: White: 34%, Black: 42%, Hispanic: 22%, Other: 2% Enrolled: 323 (survivors at 1 yr) Evaluated: 258 (at 1 yr f/up) **Sample with F/up at 2 years** Mean GA: Sample 1: 28.3 ±1.8 Sample 2: 28.1 ±1.8 Mean BW: Sample 1: 1043 ±165 Sample 2: 1005 ±184 Male: Sample 1: 49% Sample 2: 43% Race: Sample 1: White: 35%, Black: 60%, Other:5% Sample 2: White: 43%, Black: 54%, Other: 3% Enrolled: 136 (survivors at 2 yrs) Evaluated: 118 Number of sites: 2	Premature VLBW: 700-1350 g (Detailed description available in another article)	ND	At 1 yr f/up Sample 1: Synthetic Surfactant at Birth via ET tube: 5 ml/kg (136) Sample 2: Air placebo via ET tube at birth (122) At 2 yr F/up Sample 1: Synthetic surfactant at birth (57) Sample 2: Air placebo (61)	Randomized placebo-controlled double blind trial (at 1 year and at 2 years CA)

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Speechley 1995 96356544	Location: Canada Years of Birth: 1978-1980 Mean GA: Sample 1: 37 (28-43) Sample 2: 40 (37-44) Mean BW: Sample 1: 2790 (850-4550) Sample 2: 3503 (2660-5170) Male: Sample 1: 56% Sample 2: 50% Race: Sample 1: whites : 90% Sample 2: whites: 90% (Original study: was a randomized interventional study of having a family volunteer visit the home on a regular base for 6 months) Eligible (for the original study): 828 Enrolled (for the original RCT): 312 Evaluated (at 12 yrs): 253 Number of sites: 1	All infants born at a tertiary care hospital in Ontario Born between 1978-1980 Transferred to NICU or Normal Neonatal Nursery (NNN)	Family residence more than 120 Km from hospital Newborn's survival was in question Language barrier Refused to participate to the original RCT.	Sample 1: Former NICU graduates: [116] Sample 2: Former NNN graduates [137]	Prospective, longitudinal, comparative, observational study (12 yrs)

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Hack 1996 97060805	Location: US Years of Birth: 1/1977 to 12/1979 Mean GA (range), wk: 30±2 Mean BW (range), g: 1177±218 Male: ND Race: Mother black race 56% Enrolled: 249 Evaluated: 249 (363 controls) Number of sites: 1	VLBW infants, BW <1500gm, survived to 2 years of age NBW: randomly selected NBW children (the selection method was described in the prior papers)	ND	VLBW infants (249) Sample 1: AGA (199) Sample 2: SGA (50) NBW infants: (363)	Prospective cohort (8 years)
Hack 1996 97066007	Location: US Years of Birth: 7/1982-6/1988, 1/1990-12/1992 Mean GA (range), wk: Sample 1: 25.9±2 (22-31) Sample 1: 25.7±2 (22-31) Mean BW (range), g: Sample 1: 688.6±73 (560-740) Sample 2: 670.6±56 (502-742) Male: Sample 1: 28% Sample 2: 29% Race: White Sample 1: 31% Sample 2: 37% Enrolled: 280 Evaluated: 280 Number of sites: 1	BW 500-759 g Survived to 20 months corrected Age	ND	Sample 1: VLBW survived infants born in 1990-1992 (surfactant/dex era) (114) Sample 2: VLBW survived infants born in 1982-1988 (surfactant and less dex. era) (166)	Prospective cohort (followed to 20 months corrected age)

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Northern Neonatal Nursing Initiative Trial Group 1996 96304894	Location: UK Years of Birth: 1990-1992 Mean GA (range), wk: 29 (27-31) Mean BW (range), g: 1253 (965-1543) Male: 39% Race: ND Enrolled: 776 Evaluated: 776 Number of sites: 16	GA <32 weeks; resident in northern UK	ND	Experiment 1: fresh frozen plasma treatment (257) Experiment 2: gelatin plasma substitute (261) Glucose controls (258)	Randomized controlled trial (2 years)
Sethi 1996 96334245	Location: UK Years of Birth: 1989-1992 Mean GA (range), wk: ND Mean BW (range), g: ND Male: ND Race: ND SES: ND Enrolled: 93 Evaluated: 92 Number of sites: 1	Liveborn infants BW <1501 g Survived until discharged	ND	VLBW infants 92	Prospective cohort (2 years)
Wilkinson 1996 97087405	Location: Australia Years of Birth: 1/1989-12/1991 Mean GA (range), wk: 27.7 (23-34) Mean BW (range), g: 1144 (700-1725) Male: 50% Race: ND Enrolled: 12 Evaluated: 10 Number of sites: 1	All NICU admissions <35 weeks GA or BW<1500g who had cranial US with cystic PVL	ND	VLBW preterm infants (10)	Retrospective cohort

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
DeReginer 1997 98041177	Location: US Years of Birth: 1987-1991 Mean GA (range), wk: Sample 1: 28.0±1.5 Sample 2: 27.1±1.2 Sample 3: 27.5±1.7 Mean BW (range), g: Sample 1: 1030±140 Sample 2: 1007±122 Sample 3: 1007±140 Male: ND Race: ND Enrolled: 174 Evaluated: 164 Number of sites: 2	BW =1500 g survived until Discharged Able to match to a patient in other two respiratory groups	Presence of LBW independent of chronic lung disease known to adversely affect neurodevelopment, sensory, or growth, i.e. severe intracranial abnormalities, congenital anomalies or viral infections, etc. Unable to match to a patient in other groups Died after discharged (6) Lost to follow-up (4)	Sample 1: No chronic lung disease (58) Sample 2: Mild chronic lung disease (58) Sample 3: Severe chronic lung disease (58)	Retrospective chart review with marched subject group (1 year of adjusted age)
Dezoete 1997 97359687	Location: New Zealand Years of Birth: 1990-1992 Mean GA (range), wk: 26.7±1.9 Mean BW (range), g: 834.6±120.0 Male: 51% Race: European 63%, Maori 20%, Other 22% SGA: 32% Enrolled: 110 Evaluated: 105 Number of sites: 1	BW<1000g and survived to hospital discharge.	Died after discharge Congenital malformations Lost to follow-up	VLBW infants (105)	Prospective cohort (18 months)

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
O'Shea 1997 98049056 ***overlapped sample with 98190123**	Location: US Years of Birth: 1979-1994 Mean GA (range), wk: Sample 1: 25 (22-31) Sample 2: 25 (22-30) Sample 3: 25 (22-29) Mean BW (range), g: Sample 1: 673 (522-790) Sample 2: 670 (527-800) Sample 3: 688 (520-793) Male: Sample 1: 49% Sample 2: 51% Sample 3: 48% Race: White Sample 1: 61% Sample 2: 60% Sample 3: 56% Enrolled: 513 Evaluated: 513 ? 216 (1 year of age) Number of sites: 2	BW 501-800g Born to mother's residing in 17 countries in NW N.Carolina Survived to 1 year of age	ND	Sample 1: VLBW infants born between 7/1/1979 and 6/30/1984 (120 ? 24) Sample 2: VLBW infants born between 7/1/1984 and 6/30/1989 (175 ? 63) Sample 3: VLBW infants born between 7/1/1984 and 6/30/1994 (218 ? 129)	Retrospective cohort (1 year corrected age)

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Piecuch 1997 97456215	Location: US Years of Birth: 1979-1991 Median GA (range), wk: Sample 1: 25.9±1.5 (24-29) Sample 2: 25.8±1.6 (24-32) Sample 3: 26.3±1.5 (24-32) Sample 4: 27.1±1.4 (24-34) Sample 5: 27.8±1.7 (25-35) Mean BW (range), g: Sample 1: 560±28 Sample 2: 653±28 Sample 3: 747±29 Sample 4: 850±29 Sample 5: 942±30 Male: Sample 1: 25% Sample 2: 24% Sample 3: 48% Sample 4: 47% Sample 5: 48% Race: ND Enrolled: 518 Evaluated: 445 Number of sites: 2	BW<1000g Discharged from Mt. Zion Hospital + M.C. & UCSF	Genetic diagnosis {Died after discharge (14) Lost to follow-up (58) Late genetic diagnosis (1)}	Sample 1: BW 500-599 (15) Sample 2: BW 600-699 (38) Sample 3: BW 700-799 (92) Sample 4: BW 800-899 (135) Sample 5: BW 900-999 (165)	Prospective cohort (1 year)

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Piecuch 1997 98012134	Location: US Years of Birth: 1990-1994 Mean GA (range), wk: Sample 1: 24 Sample 2: 25 Sample 3: 26 Mean BW (range), g: Sample 1: 668±91 (450-850) Sample 2: 790±115 (550-1000) Sample 3: 842±158 (505-1260) Male: Sample 1: 50% Sample 2: 73% Sample 3: 50% Race: ND SES: high social risk Sample 1: 89% Sample 2: 43% Sample 3: 68% Enrolled: 94 Evaluated: 86 Number of sites: 1	24, 25 or 26 week GA Non-anomalous Born at University of California, San Francisco	ND (Died after discharge (2) Accidental severe central nervous system insult after discharge (1) Lost to follow-up (5)}	Sample 1: GA 24 weeks (18) Sample 2: GA 25 weeks (30) Sample 3: GA 26 weeks (38)	Prospective cohort (at 12months, 18 months, 2 ½ years, 4 ½ years. 7-8 years)

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Singer 1997 98049057 Singer 2001 21163669	Location: US Years of Birth: 1989-1991 Mean GA (range), wk: Sample 1: 27±2 Sample 2: 30±2 Controls: 40±2 Mean BW (range), g: Sample 1: 956±248 Sample 2: 1252±178 Controls: 3451±526 Male: Sample 1: 52% Sample 2: 43% Controls: 50% Race: White Sample 1: 55% Sample 2: 48% Controls: 51% SES: Hollingshed classification: Sample 1: 3.5±1 Sample 2: 3.6±1 Controls: 3.6±1 Enrolled: 464 Evaluated: 206 (123 controls) Number of sites: 3	Cases (sample 1&2): premature infants, BW < 1500g Controls: term infants with no diagnosed medical illness or abnormalities at birth, >36 weeks, GW>2500g	Major congenital abnormality Drug exposure Maternal illness HIV Maternal mental retardation >2 hours driving time from hospital	Sample 1: VLBW infants with BPD infants (122) Sample 2: VLBW without BPD (84) Sample 3: Full term infants (123)	Prospective cohort (followed to 3 years corrected age)

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Victorian Infant Collaborative study Group, 1997 98026322 ***This study is also in CNS table**	Location: Australia Years of Birth: 1979-80, 1985-87, 1991-92 Mean GA (range), wk: ND Mean BW (range), g: ND Male: ND Race: ND Enrolled: 453 (242 controls) Evaluated: 448 (242) Number of sites: 3	ELBW infant (Sample 1-3ts, BW 500-999 g born in Victoria, Australia survived to age of 2 years Controls: Normal birth weight (>2499 g) infants born in 1991-1992	Excluded infants born in 1979-1980 for current review	ELBW infants (448): Sample 1: born in 1985-1987 (212) Sample 2: born in 1991-1992 (241) Controls: Normal BW (>2499 g) infants (242)	Retrospective cohort (2 years)
Victorian Infant Collaborative study Group, 1997 97466059	Location: Australia Years of Birth: 1979-80, 1985-87, 1991-92 Mean GA (range), wk: ND Mean BW (range), g: ND Male: ND Race: ND Enrolled: 36 Evaluated: 35 Number of sites: 3	ELBW infants, BW 500-999 g born outside the level III perinatal centers in Victoria, Australia survived to age of 2 years	Excluded infants born in 1979-1980 for current review	ELBW infants (36): Sample 1: born in 1985-1987 (19) Sample 2: born in 1991-1992 (16)	Retrospective cohort (2 years)
Cheung 1998 99059896	Location: Canada Years of Birth: 12/93-10/97 Mean GA (range), wk: 25 (24-30) Median BW (range), g: 860 (340-1460) Male: 67% Race: ND Enrolled: 24 Evaluated: 10 Number of sites: 1	VLBW survivors, BW < 1500 g, Requiring inhaled nitrous oxide (INO) (continues to be hypoxenic) at >90% O_2 and MAP 15 $\pm$ 2)	Mosaic trisomy 18 Potter's syndrome Survived to 1 year of chronological age	VLBW infants treated with INO (10)	Prospective cohort

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Finnström 1998 99041345	Location: Sweden Years of Birth: 1990-1992 Mean GA (range), wk: ND Mean BW (range), g: 798±144 Male: ND Race: ND Enrolled: 370 Evaluated: 362 Number of sites: ND	BW = 1000 g and GA = 23 weeks Survived to the age of 1 year	ND	Preterm infants (362)	Prospective cohort of a previously published study (followed to the median corrected age of 36 months)
Gregoire 1998 98232532	Location: Canada Years of Birth: 1987-1992 Mean GA (range), wk: Sample 1: 27.3±1.1 Sample 2: 26.8±1.3 Comparison: 27.9±0.8 Mean BW (range), g: Sample 1: 997±195 Sample 2: 930±178 Comparison: 1129±181 Male: Sample 1: 45% Sample 2: 56% Comparison: 45% Race: ND Enrolled: 217 Evaluated: 217 Number of sites: 1	Inborn infants GA 24-28 weeks, Admitted to NICU Survival to 18 months CA	ND	Sample 1: BPD-1 group – preterm infants who received O_2 at 28 days but not at 396 weeks' GA (48) Sample 2: BPD-2 group – preterm infants with oxygen dependency at 36 weeks' GA (93) Comparison: preterm infants who were not oxygen-dependent at 28 days of age (76)	Prospective cohort (18.5±1.1 months)

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Kurkinen-Raty 1998 98387235 (All+Lung) ***sample from the same big population as 20284814**	Location: Finland Years of Birth: 1990-1996 Mean GA (range), wk: Cases: 28.2 (23.8- 37.2) Controls: 28.4 (22.9-36.9) Mean BW (range), g: Cases: 1138.3±434 Controls: 1272.4±547.2 Male: ND Race: ND Enrolled: 78 (78 controls) Evaluated: 78 (78) Number of sites: 1	Preterm PROM between 17-30 weeks gestation; singleton; delivered > 2 hr after rupture Controls: preterm no PROM; spontaneous preterm delivery matched for GA and year of delivery.	Rupture unconfirmed or transient	Sample 2: Preterm rupture (78) Sample 2: Preterm delivery no rupture (78)	Retrospective cohort

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Lee 1998 98442293	Location: Canada Years of Birth: 1990-1995 Mean GA: ND Mean BW: Sample 1: 763 ±157 Sample 2: 807±176 Male: ND Race: ND Enrolled: ND (total N not given, data only for enrolled cases with candidemia: N= 29) Evaluated: 50 Assessed for outcome: 35 (14 cases and 21 controls) Number of sites: 2	For cases: Prematures with BW<1250 g Admitted in the NICU s of UAH and RAH from 1990-1995 Diagnosis of candidemia: by at least one positive blood culture Diagnosis of candidal meningitis: By isolation of candida in the CSF or >45x10 ^{6} WBCs in the CSF and candidemia. For controls: Prematures with BW <1250 g Admitted to the same NICUs during the same period without candidal infection	Neonates with major congenital anomalies	Sample 1: Premature infants <1250 with candidemia and/ or candida meningitis (25) Sample 2: Premature neonates with BW <1250 matched with cases for BW, GA, sex and admission dates, without candidal infection (25)	Retrospective longitudinal comparative study with case control design and cases defined based on exposure to candidemia and matched controls (f/up between 37 and 70 mo CA) Average age at assessment: for cases :31 ±19 mo, and for controls: 28 ±20 mo
Lefebvre 1998 98387703	Location: Canada Years of Birth: 1987-1992 Mean GA (range), wk: 27.0±1.2 Mean BW (range), g: 961±179 (585-1450) Male: 52% Race: ND Enrolled: 139 Evaluated: 121 Number of sites: 1	GA<28 weeks 3 or more cranial ultrasounds Survival to discharge	ND	Preterm infants (121): Low risk (50) Moderate risk (37) High risk (34)	Prospective cohort (CA 18.6±1.2 [17-19] months)

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Millet 1998 98212544	Location: France Years of Birth: ND Mean GA (range), wk: 31±3 (25-36) Mean BW (range), g: 1243±400 Male: 75% Race: ND Enrolled: 60 Evaluated: 40 (20 controls) Number of sites: 1	Neonates considered at risk of neurologic impairment	Severe neurologic abnormalities (HIE, PVL, brain malformations and congruental infections)	Premature infants (40) Term infants (20)	Prospective cohort (3-6 months correlated age)

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Piecuch 1998 98446413	Location: USA Years of Birth: Sample 1: 1989-1991 Sample 2: 1984-1986 Sample 3: 1979-1981 Mean GA: Sample 1: 29 ±2 Sample 2: 30 ±2 Sample 3: 30 ±2 Mean BW: Sample 1: 1221 ±142 Sample 2: 1235 ±140 Sample 3: 1246 ±146 Male: Sample 1: 56% Sample 2: 50% Sample 3: 46% Race: ND Enrolled: 563 Evaluated: 450 Number of sites: 4	Prematurity BW: 1000-1499 g Discharged from NICUs of 5 Hospitals Born in one of the three time periods: 1989-1991 (Recent) 1984-1986 (Middle) 1979-1981 (Early)	Congenital anomalies	Comparison of the outcome of infants 1000-1499 g born in three time periods: Most recently born Born at a middle period Born at an early period Sample 1: Born most recently, between 1989-1991 (186) Sample 2: Born in a middle period, between: 1984-1986 (155) Sample 3: Born in an early period, between 1979-1981 (109)	(Not clearly stated) Retrospective longitudinal comparative cohort study Age for outcome assessment was not specified. It could be done up to 7.5-8 yrs of age (Mean ages of f/up were: 24, 54, 75 mo for the 3 periods)

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Sajaniemi 1998 99041674	Location: Finland Years of Birth: 1989-1991 Mean GA: Sample 1: 28.9 (23-35) Sample 2: 39.4 (36-43) Mean BW: Sample 1: 1205 (560-2360) Sample 2: 3461 (2510-5360) Male: ND Race: ND Enrolled: ND Evaluated : 160 Number of sites: 1	For Preterm Group (sample 1): GA: 23-34 wks Mother being referred to University Central Hospital of Helsinki for threatened preterm delivery Born between 1989-1991 For Full term group (Sample 2): Born in Metropolitan Helsinki Visiting pediatric services in Helsinki for acute infectious diseases	For Preterm group If mothers had chorioamnionitis If mother had insulin dependent diabetes Children with congenital anomalies, by U/S For Full term group Chronic diseases Developmental delay	Sample 1: Preterm infants (80) Sample 2 Full term enrolled at: 20-28 mo of age (80)	Retrospective comparative study (24 mo CA)
Scherjon 1998 98429216	Location: Netherlands Years of Birth: 1989 Mean GA: ND [median and range given: 30.4 (26.1-32.8)] Mean BW: ND (median and range given: 1295 (605-2295)] Male: ND Race: ND Enrolled: 106 Evaluated: 96 (at 3 yrs) Number of sites: 1	Pregnant mother admitted to Obstetric Department of Amsterdam university with threatened preterm delivery GA < 33 wks. Admitted during a 10 month period in 1989	Pregnancies with known congenital or chromosomal anomalies	Infants born prematurely between 26-33 wks (96)	Prospective observational cohort study (3 yrs CA)

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Cheung 1999 99146391	Location: Canada Years of Birth: 1990-1993 Mean GA (range), wk: Sample 1: 25 (22-29) Sample 2: 26 (24-30) Sample 3: 28 (23-32) Mean BW (range), g: Sample 1: 660±56 Sample 2: 873±73 Sample 3: 1127±71 Male: total 57% Race: ND Enrolled: 187 Evaluated: 164 Number of sites: 2	BW<1250 gm GA < 32 weeks Mild or no significant respiratory disease (O_2 < 30%, RR < 70)	Major congenital abnormalities, syndromes Infants with neurologic insult after discharge from NICU.	Sample 1: BW 500-749 g (26) Sample 2: BW 750-999 g (63) Sample 3: BW 1000-1249 g (75)	Prospective cohort (followed to 24 months adjusted age)
Duvanel 1999 99207097	Location: Switzerland Years of Birth: 1982-1990 Mean GA: Sample 1: 31.9 ±2.1 Sample 2: 31.9 ±1.7 Mean BW (range) Sample 1:1142 ±285 Sample 2: 1186 ±229 Male: Sample 1: 47% Sample 2: 57% Race: ND Enrolled: : ND Evaluated: 85 Number of sites: 1	Prematurity (< 34 weeks GA) SGA (BW < 10% percentile) Cases: hypoglycemia: glucose level < 47 mg/dl Controls-matched: (not specified for which parameters): blood glucose > 47 mg/dl .	Major malformations Metabolic diseases Periventricular leukomalacia Grade IV cerebral hemorrhage Psychiatric illness detected in follow up study Very low socioeconomic status	Sample 1 Hypoglycemic (62) Sample 2: Euglycemic (23)	Retrospective longitudinal cohort study with case control design. Cases defined based on exposure. Control group matched with cases (not specified for which parameters)

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Pennefather, 1999 20002011 Pennefather, 2000 20217908 *** This study is also in eye table**	Location: UK Years of Birth: 1/1/90-12/31/91 Mean GA (range), wk: ND Mean BW (range), g: ND Male: ND Race: ND Enrolled: 566 Evaluated: 558 Number of sites: ND	All surviving children <32wk GA born in geographically deprived region in Northern UK Survived to 2 years old	No examined at age 2 years old	Preterm infants (558)	Prospective cohort and retrospective review of patient records (2-3 years)
Ambalavanan 2000 21031370	Location: US Years of Birth: 1/1990 to 12/1994 Mean GA (range), wk: 26±2 Mean BW (range), g: 829±123 Male: 45% Race: African-American 66% Enrolled: 218 Evaluated: 218 Number of sites: 1	ELBW infants, BW <1000 g	ND	ELBW infants (218)	Retrospective cohort (followed to 18 months of age)
Cioni 2000 20150341	Location: Italy Years of Birth: 1/1989 to 2/1994 Mean GA (range), wk: 31±2.8 (24-36) Median BW (range), g: ND Male: ND Race: ND Enrolled: 29 Evaluated: 29 Number of sites: 1	All premature newborns with brain lesions on HUS who have abnormal neurological exam at term who are enrolled in neonatal follow–up study	Severe ROP (≥ stage 3), major refraction problems, and optic nerve atrophy, and infants with "congenital diseases"	All premature newborns with brain lesions who have abnormal neuro-logical exam at term (29)	Prospective cohort (1 yr [8-16 months] and 3 years [30-47 months])

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Hack 2000 20358826	Location: US Years of Birth: : 1/1/1992-2/31/1995 Mean GA (range), wk: 26.4±1.8 Mean BW (range), g: 813±125 Male: 43% Race: ND Enrolled: 333 Evaluated: 221 Number of sites: 1	BW<1000g	Major congenital malformations	VLBW infants (221)	Prospective cohort
Jankov 2000 20188680	Location: Canada Years of Birth: 1990-1996 Mean GA (range), wk: Sample 1: 23 (20-28) Sample 2: 25 (23-33) Mean BW (range), g: Sample 1: 669 (400-750) Sample 2: 515 (255-745) Male: Sample 1: 51% Sample 2: 46% Race: ND Enrolled: 281 Evaluated: 269 Number of sites: 1	Infants = 750 g and GA = 20 weeks who received CPR in the delivery room	Charts were not available for review (5) Major congenital abnormalities (4) Those infants not intubated in the delivery room (3)	Sample 1: Resuscitated (198) Sample 2: Non-resuscitated (71)	Retrospective cohort

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Kurkinen-Raty, 2000 20284814 ***sample from the same big population as 98197235**	Location: Finland Years of Birth: 1990-1997 Mean GA (range), wk: Cases: 30.5±2.1 Controls: 30.4±2.1 Mean BW (range), g: Cases: 1294±469 Controls: 1605±427 Male: ND Race: ND Enrolled: 103 (103 controls) Evaluated: 103 (103) Number of sites: 1	Cesarean delivered singleton, GA 24-33 weeks Controls: spontaneous delivered singleton after regular contractions and/or preterm rupture of the membranes no more than 24 hrs before. The mothers were matched one-to-one by gestational age at delivery plu7s or mines 1 week.	ND	Sample 1: Indicated preterm (i.e., preterm birth 'indicated' for maternal/fetal reasons)(103) Sample 2: Spontaneous preterm delivery due to preterm labor (103)	Retrospective cohort

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Marlow 2000 20150342	Location: UK Years of Birth: 1990-1994 Mean GA: ND (Median and Range) Sample 1: 28 (26-31) Sample 2: 28 (26-31) Mean BW: ND (Median and range) Sample 1: 960 (600-2914) Sample 2: 1026 (410-2814) Male: ND Race: ND Enrolled : 27 Evaluated: 15 Number of sites: 1	For sensorineural hearing loss (SNHL) group GA: <33 wks Family resident of Greater Bristol area Records at Hearing Assessment Center of Royal Hospital for Sick children. Born during 1990-1994 Diagnosis of SNHL of 50 dB For control group: Matched controls 2:1 to cases Admitted to the same NICUs as cases Matched for sex and GA and next and preceding matching children in the admission books of St Michael's and Sothmead hospitals	ND	Sample 1: SNHL group [15] Sample 2: Control group [30] Matched with cases for sex, GA, admission dates in NICU	Retrospective case control study with a longitudinal component (unclear if retrospective or prospective) (12 mo CA)

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Victorian Infant Collaborative study Group, 2000 20307288 ***some subjects overlapped with Doyle, 2001**	Location: Australia Years of Birth: 1991-92 Mean GA (range), wk: Sample 1: 25.5±1.3 Sample 2: 27.3±1.9 Mean BW (range), g: Sample 1: 797±147 Sample 2: 932±149 Male: Sample 1: 61.2% Sample 2: 39.5% Race: ND Enrolled: 346 Evaluated: 346 Number of sites: 4	BW<1000 or GA<28 consecutive births, survived to 5 years of age	ND	Preterm infants (120): Sample 1: infants treated with corticosteroids Sample 2: infants not treated with corticosteroids (226)	Non-randomized comparison trial (5 years)
Wood 2000 20373840	Location: UK and Ireland Years of Birth: 1995-1996 Mean GA (range), wk: 22-25 Mean BW (range), g: ND Male: ND Race: ND Enrolled: 314 Evaluated: 283 Number of sites: 276	GA 20-25 weeks survivors	ND	Preterm infants (283)	Prospective cohort (30 [28-40] months)

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Doyle 2001 21326609 Victorian Infant Collaborative study Group, 1997 97290716 J Paediatr Child Health ***some subjects were overlapped with 20307288 (stated in text)** ***possibly overlapped with 98026322**	Location: Australia Years of Birth: 1991-92 Mean GA (range), wk: 23-27 Mean BW (range), g: ND Male: ND Race: ND Enrolled: 225 Evaluated: 225 (265 controls) Number of sites: 1	Cases: GA 23-27 weeks, survived to 2 and 5 years of age Controls: randomly selected contemporaneous normal birth weight controls (BW > 2499 g)	ND	Sample 1: Preterm survivors (N= 401) Controls: Randomly selected contemporaneous normal birth weight controls (BW>2499 grams) (N=265)	Prospective cohort (Doyle - 5 years; Victorian – 2 years)

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Gaillard 2001 21221175	Location: UK Years of Birth:1994-1996 Mean GA: ND (only median and range given) Sample 1: 26 (23-34) Sample 2: 26 (23-33) Mean BW: ND (only median and range given) Sample 1: 852 (520-2710) Sample 2: 745 (580-1620) Male: Sample 1: 57% Sample 2: 50% Race: ND Enrolled: 100 Evaluated: 84 Number of sites: 1	Retrospective cohort : All infants born from 1/1/1994 to 12/31/1996 Born at Liverpool Women's Hospital Ventilated beyond 27 postnatal days	If transferred from another hospital after first postnatal week (mostly surgical referrals) If ventilated after 27 postnatal days after a surgical procedure requiring anesthesia	Sample 1 : Ventilated beyond 27 (but not 50) postnatal ds (56) Sample 2: Ventilated beyond 49ds (28)	First component: Retrospective longitudinal cohort with case-control design and cases defined based on exposure (length of ventilation). Unmatched. (3 years) Second component: Retrospective longitudinal cohort study With two historical control groups (3 years)
Roth 2001 21262686	Location: UK Years of Birth: 1979-1988 Mean GA (range), wk: Sample 1: 29 (24-32) Sample 2: 29 (24-32 Mean BW (range), g: Sample 1: 1350 (600-2500) Sample 2: 1324 (535-2390) Male: Sample 1: 49% Sample 2: 53% Race: ND Enrolled: 854 Evaluated: 782 Number of sites: 1	GA < 33 weeks During 1980, for logistic reasons, only infants who were either less than 1250 g or mechanically ventilated were enrolled	ND	Sample 1: children had been studied by linear array US scanning (205) Sample 2: children had been studied by mechanical sector scanning (577)	Retrospective cohort (followed to age of 7 years and 2 months, and 10 years and 6 months)

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Saigal 2001 21376729 *** Important paper**	Location: Canada Years of Birth: 1977-1982 Mean GA (range), wk: Cases: 27±2 Controls: "Term" Mean BW (range), g: Cases: 835±124 Controls: 3401±481 Male: Cases: 31% Controls: 36% Race: ND SES: middle class Cases: 30% Controls: 30% Enrolled: 179 (145 controls) Evaluated: 154 (125) Number of sites: 1	ELBW survivors, BW= 501-1000g Controls: term infants recruited at 8 years of age from a random list obtained through the directors of 2 school boards and matched for gender, age, and SES to each case	ND (Died after discharge (10) Lost to follow-up (8) Refusal (5) Unable to be reached (2) Controls: Lost to follow-up (10) Refusal (8) Unable to be reached (2))	Cases: ELBW infants (154) Controls: Term infants (125)	Prospective cohort (followed to 12-16 years age)

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Schmidt 2001 21298249	Location: Canada, USA, Australia, New Zealand, Hong Kong Years of Birth: 1996-1998 Mean GA: Sample 1: 25.9 ±1.8 Sample 2: 26 ±1.9 Mean BW: Sample 1: 782 ±131 Sample 2: 783 ± 130 Male: 51% Race: Sample 1:White: 69%, black: 13%, Asian: 5%, other: 12% Sample 2: White: 67%, black: 14%, asian: 7%, other: 12% Enrolled: 2756 Evaluated: 1202 Number of sites: 32	BW: 500-999g 2 hrs old Born in 1 of the 32 participating centers in Canada, USA or Australia. Born during 1/1996-3/1998	Excluded total 981 (not eligible) Unable to administer study drug within 6 hrs of birth , n=469 Structural heart disease Renal disease or both, or strongly Suspected (n=24) Dysmorphic feature or congenital abnormalities likely to affect life expectancy or neurologic development or to be associated with structural heart disease or renal disease (n=49) Maternal tocolytic therapy with indomethacin or another prostaglandin inhibitor within 72hr before delivery (n=245) Overt clinical bleeding at more than one site (n=8) Platelet count <50.000 (n=25) Hydrops (n=9) Not considered viable (n=171) Unlikely to be available for f/up (n=31)	Sample 1: Indomethacin group [574] Sample 2: Placebo group [569]	Randomized, multicenter, placebo/controlled, double-blind trial (18 mo CA)

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Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Akerman 1992 93255928	General: BW, GA, Twinning Other: Mother's negative or ambivalent expectations concerning the twin pregnancy	Interviews with mother prior to delivery	**CNS:** Motor delay Cognitive delay Behavioral disorders **Ophthalmology**: Visual Impairment **Audiology:** Deafness Speech	Griffith's Mental Development Scales: including locomotor, personal-social, hearing and speech, hand and eye coordination, performance, and practical reasoning scores
Thompson 1993 93234177	Birth weight GA	ND	**CNS:** Motor delay CP Cognitive delay Mental retardation **Ophthalmology:** Visual impairment **Audiology:** Hearing disorders	Griffith's scale
Rademaker 1994 95003452	CNS: 1) Intracranial / Intraventricular hemorrhage 2) White Matter Disorder 3) Periventricular leukomalacia	US grading GLH-IVH	**CNS:** Cognitive delay Mental retardation Post Hemorrhagic Hydrocephalus (PHH) **Ophthalmology:** Visual impairment **Audiology:** Hearing disorders	Griffith's mental development scale Amiel-Tison, Greniers and Touwen scores IQ

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Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Vonderveid 1994 94297368	General: 1) BW (in 100 g intervals) 2) GA (in wks) 3) Gender 4) SGA(<10% vs > 10%) 5) Type of pregnancy 6) Fetal presentation 7) Antenatal steroid 8) Place of birth 9) Apgar score 1 min 10) Apgar score 5 min 11) Transport 12) On admission to NICU: Spontaneous respirations (present or absent); Body temperature (<35 vs >35); PH (<7.00 vs 7.00-7.09 vs > 7.09); PCO2: 80 vs 60-79 vs 40-59 vs <40 Pulmonary: 1) RDS 2) Maximum FIO2 required CNS: 1) Peri-intra-ventricular hemorrhage 2) PVL Others: 1) Sepsis 2) Maximum bilirubin level 3) Hypoglycemia (< 25 mg/dl) 4) Hyperglycemia (>175 mg/dl) 5) Acidosis (pH<7.20)	ND	**CNS – Audiology-Ophthalmology:** 1) Neuromotor disorders: ➢ impairment ➢ disability ➢ handicap ➢ (including CP, Blindness, Deafness) 2) Developmental quotients	1) Each limb was evaluated separately: ➢ 0= nl function ➢ 1= impairment with no loss of function ➢ 2= mild motor disability ➢ 3= severe motor disability ➢ 4= complete loss of function 2) Cerebral palsy: Monoplegia, diplegia, paraplegia, hemiplegia, quadriplegia) 3) Developmental quotients: Brunet-Lezine test (24 mo CA)

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Kraybill 1995 95264242	**General:** 1) Surfactant (single dose 5 ml/kg given via ET tube at birth)	Infants were treated, as soon as after birth, either with 5 ml/kg of surfactant or air placebo, via ET tube.	1 yr assessment (NCMH and HCHD cohort): **General:** Overall survival **Pulmonary:** Need for O2 via Nasal canula Need for O2 via CPAP CLD 2 yr assessment (NCMH cohort only) **General:** Overall survival Hospitalization for respiratory illness **Pulmonary:** Bronchodilator regular use Tracheostomy 1 and 2 yr assessment: **Growth:** Height for age Weight for age HC for age Mean MDI score MDI scores < 2 SDs Mean PSI score PDI scores < 2 SDs Severity of impairments Types of Impairments Any surgery Assessment between 28 ds-12mo: **Ophthalmology:** ROP Tx for ROP ROP presence at latest exam Severe ROP	No further specifications given, except for the followings: Oxygen via Nasal canula : providing alveolar O2 concentrations of : 26%-40%, based on NC flow and NC O2 concentration Bayley Scale of Infant Development: 1) MDI= Mental Development Index Score 2) PDI: Psychomotor Development Index Score ROP : (no further definitions) 1) No ROP, 2) Mild/moderate 3) Severe CP (no further definitions) 1) Mild 2) Moderate/Severe Severity of impairments: 1) Severe 2) Mild/Moderate Types of impairments: 1) MDI<69 2) MDI: 69-84 3) Moderate/severe CP 4) Mild CP 5) Bilateral sensorineural deafness 6) Deafness not requiring amplification 7) Bilateral blindness 8) Visual defect (1 yr and 2 yr CA)

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Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Speechley 1995 96356544	General: 1) Former NICU graduate (of any BW) 2) Gender	Not further specified	Physical health outcome at 12 yrs 1) Chronic physical health (mother's report) 2) Lifetime hospitalizations (mother's report) 3) Physical impairments (mother's report) 4) Perception of child's heath (child's report) 5) Perception of child's health (mother's report) Emotional and social wellbeing at 12 yrs: 1) Internalizing problems (child's report) 2) Externalizing problems (child's report) 3) Social competence (child's report) 4) Social support (child's report) 5) Self esteem (child's report) 6) School performance (mother's report)	Based on responses on an interviewer administered and self-report questionnaire. Physical health outcome at 12 yrs 1) Chronic physical health (mother's report): Precoded 25 chronic illnesses 2) Lifetime hospitalizations (mother's report) 3) Physical impairments (mother's report):response to a question asking whether their child had any physical impairments 4) Perception of child's heath (child's report): 4-item scale 5) Perception of child's health (mother's report): 4-item scale Emotional and social well being at 12 yrs: 1) Internalizing problems (child's report) 3-item scale 2) Externalizing problems (child's report) 3-item scale 3) Social competence (child's report) 36-item scale 4) Social support (child's report) 24-item scale 5) Self-esteem (child's report) 10-item scale 6) School performance (mother's report) 5-item scale

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Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Hack 1996 97060805	General : 1) VLBW vs. NBW 2) GA 3) SGA/IUGR 4) Sex CNS: Neurosensory Development IA+II, I Other: Maternal Factors, race, education, height, martial	VLBW<1500gm (AGA+SGA) to compare growth with FT NBW infants	**CNS:** Major neurosensory abnormal. **Growth:** Weight Height Head Circumference	ND
Hack 1996 97066007	General: Birth Weight	500-750 gm	**CNS:** Cerebral palsy Motor and cognitive delay **Ophthalmology:** Blindness **Audiology:** Deafness	Neurosensory status BSID: MDI, PDI

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Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Northern Neonatal Nursing Initiative Trial Group 1996 96304894	Cardiovascular or Pulmonary Predictors: use of FFP or plasma substitute to expand vascular volume prophylactically	ND	**CNS Outcomes:** Motor delay Cerebral palsy Seizure disorder Post hemorrhagic hydrocephalus **Ophthalmology:** Visual impairment Blindness **Audiology Outcomes:** Hearing disorders Speech **Other outcomes:** a. blind, deaf, or unable to walk – combined outcome b. no severe disability – combined outcome c. overall developmental quotient – Griffith's	Motor delay: Griffith's gross motor quotient >350 below mean Griffith's quotient for speech + hearing >350 below mean
Sethi 1996 96334245	General Predictors: 1) Birth weight	1) 2) <1000g 3) 1000g - 1500 g	**CNS Outcomes:** Cerebral palsy Cognitive delay Seizure disorder **Ophthalmology outcomes:** Blindness ROP - eye exam **Audiology outcomes:** Deafness **Other outcomes:** Survival	"abnormal neurodevelopmental outcome" - not defined "major impairment" - any CP blindness, deafness, "significant" developmental delay or hydrocephalus requiring a shunt deafness OAE testing before discharge and at 7 months "minor impairment" - squint, refractive error, mild auditory impairment (< 50 dB loss), stable epilepsy, or needing speech therapy assessment

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Wilkinson 1996 97087405	CNS predictors: Periventricular leukomalacia (severe cystic PVL)	Changes not seen on first scan Multiple cysts must be present (excludes cases with flare only) The cysts are bilateral The cysts are distributed in the periventricular area involving the region of the trigones and variable involvement anterior to the trigones	**CNS outcomes:** Motor delay Cerebral palsy Cognitive delay Mental retardation **Ophthalmology outcomes**: Visual impairment Blindness **Audiology outcomes:** Hearing disorders	Not specifically defined. Spastic quadriparesis, cortical blindness, seizures presumably self-evident.
DeReginer 1997 98041177	Cardiovascular/ Pulmonary: Chronic lung disease	Classification based on the duration of supplemental oxygen requirements. "No CLD" – breathing room air at 28 days "Mild CLD" – requiring supplemental oxygen at 28 days but not at 36 weeks PMA Sever CLD" – requiring oxygen at 28 days and 36 weeks PMA	**General:** Motor and cognitive delay Cerebral palsy **Opthalmology:** Visual impairment Blindness **Audiology:** Hearing loss Deafness **Growth:** Weight Z score Length Z score Head circumference Z score **Other:** any adverse outcome	Bayley PDI & MDI

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Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Dezoete 1997 97359687	General: 1) Birth weight 2) GA 3) SGA/IUGR CNS: Intracranial/Intraventricular Hemorrhage Cardiovascular/ Pulmonary: Chronic Lung disease	Clinical measures	**CNS:** Motor delay Cerebral palsy Cognitive delay **Ophthalmology:** Visual impairment Blindness **Audiology:** Deafness	Stratify outcome into 4 categories base on severity of 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). 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. Category III – Presence of tone disorder or motor delay (adjusted Bayley motor score more than one SD below mean but adjusted mental score within average rage.) Category IV / "apparently normal" – (1) No apparent tone disorder, and (2) No apparent developmental delay when mental and motor scores adjusted for GA.

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Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
O'Shea 1997 98049056 ***overlapped sample with 98190123**	General: BW, GA, Yr of birth CNS: 1) Intracranial/ Intraventricular hemorrhage 2) White matter disorder 3) Periventricular leuko-malacia	Hemorrhage disease diagnosed by cranial US finding, classified by Stewart's method	**CNS:** Cerebral palsy Cognitive delay Major neurosensory impairments **Ophthalmology:** Blindness **Growth:** Head Circumference<10th percentile at 1 yr Weight<10% Length<10% **Other:** Rehospitalization	CP – presence of definitely abnormal position and posture attributable to impaired neuromotor function Bayley scales – MDI, PDI
Piecuch 1997 97456215	General: 1) Birth weight 2) GA 3) SGA/IUGR 4) Social Risk CNS: Intracranial/Intraventricular Hemorrhage, Periventricular leukomalacia Cardiovascular/Pulmonary: Chronic lung disease Other: 1) Inborn-Outborn 2) Year of birth 3)Sex	Well defined in text	**CNS:** Motor delay Cerebral palsy Cognitive delay **Ophthalmology:** Visual Impairment **Audiology:** Hearing Disorder	Neuromotor problems, OP Neurosensory-blindness/hearing loss Cognitive outcome-abnormal if <2 SD below mean testing

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Piecuch 1997 98012134	*General predictors:* 1) GA *CNS predictors:* 1) intracranial/ intraventricular hemorrhage 2) periventricular leukomalacia *Cardiovascular or pulmonary predictors:* 1) chronic lung disease *Other predictors:* 1) social risk: economic 2) social risk: substance abuse	CLD - at 36 weeks PCA, requirement for supplemental O_2 IVH grade 3 or 4 & PVL, according to sonogram Social risk economic - maternal education <12 grade; complete unemployment in household; or government assistance for health insurance Social risk substance abuse - positive toxicology screens or confirmed history of drug or alcohol abuse	**CNS outcomes:** cerebral palsy cognitive delay **Ophthalmology outcomes:** visual impairment **Audiology outcomes:** hearing disorders	Visual – Near point tests or Snellen eye charts Audiologic - behavioral testing followed by BAER or pure tone audiometry. Cognitive outcome - Bayley scales at 12 and 18 months; Stanford-Binet at 2.5-4 years; McCarthy scales at 4-6 years. Abnormal neurological outcome - CP, quadriplegia, dysplegia, hemiplegia Suspicious neurological outcome – clumsiness, tremors Severe neurosensory abnormalities – Bilateral hearing loss, blindness Mild neurosensory abnormalities - high frequency hearing loss without hearing aids, visual deficit without glasses
Singer 1997 98049057 Singer 2001 21163669	Cardiovascular or pulmonary predictors: 1) Bronchopulmonary dysplasia General : BW, Neurologic risk Other: Race, Socioeconomic status	BPD: preterm,<1500g BW, oxygen for >28 days with radiographic evidence of CLD	**CNS outcomes:** Cerebral palsy Cognitive delay Mental retardation **Ophthalmology outcomes:** Visual impairment **Audiology outcomes:** Hearing disorders Speech Language Communication disorder	Bayley Scales of Infant Development Language (speech/communication) measured by Battelle Developmental Communication Subscale Domain→ receptive, expressive and total communication scores converted to DQ mean 100 and SD 15.

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Victorian Infant Collaborative study Group, 1997 98026322 ***This study is also in CNS table**	General: BW Other: period of time when born	Each sample were subdivided into BW=500-749 g and BW=750-999 g 1985-1987 vs. 1991-1992	**CNS:** Cerebral palsy Neurodevelopmental: Cognitive and motor delay Disability **Ophthalmology:** Blindness **Audiology**: Deafness or hearing aid	CP was not defined Bayley Scales of Infant Development DQ, using the published mean and SD Disability: "Severe" – bilateral blindness, cerebral palsy with the child unlikely ever to walk, or a DQ score <-3SD; "Moderate" – bilateral sensorineural deafness requiring hearing aids, cerebral palsy in children not walking at 2 but expected to walk, or a DQ score from –3SD to <-2 SD; "Mild" – cerebral palsy but walking at 2 , or a DQ score form –2 SD to <-1 SD.
Victorian Infant Collaborative study Group, 1997 97466059	Other: time period of birth	ND	**CNS:** Cerebral Palsy Cognitive delay Post Hemorrhagic Hydrocephalus (PHH) Ophthalmology: Blindness **Audiology**: Deafness **Other:** Sensorineural disability: severe, mental, moderate, none.	CP neurologic exam Bayley MDI, PDI scores Blindness-not stated Deafness-not stated Degrees of sensorineural delay are defined as an aggregate measure and are approximated.

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Cheung 1998 99059896	Cardiovascular or Pulmonary Predictors: Inhaled nitric oxide (INO)	ND	**CNS Outcomes:** Post Hemorrhagic Hydrocephalus (PHH) "Neurodevelopmental outcomes" Intraventricular hemorrhage **Audiology Outcomes:** Deafness **Pulmonary Outcomes:** BPD or CLD (with or without meds) Aspiration pneumonia **Growth Outcomes:** Wt, HC, length (height)	PDI + MDI of Bayley Scales of Infant Developmental Index were used. "Neurodevelopmental" outcomes: Disability: one of more of: 1. CP (all types or severity) 2. Legal blindness (corrected visual acuity of the better eye <20/200 3. Hearing loss (sensorineural hearing loss of >30 dB in the better ear) 4. Severe mental retardation (MDI >3 SD below the mean) Delay: does not have disability and either MDI or PDI was >2 SD below the mean. Normal: free of disability or delay and MDI and PDI were within 2 SD of the mean.

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Finnström 1998 99041345	General Predicators 1) GA 2) SGA/IUGR 3) Apgar score 4) Other: gender CNS Predicators 1) Intracranial/Intraventricular hemorrhage 2) Periventricular leukomalacia Ophthalmology Predicators 1) Retinopathy of Prematurity (ROP) Cardiovascular or Pulmonary Predictors 1) Chronic Lung Disease 2) Other: Mechanical ventilation Other Predicators 1) Other: PDA	Self-explanatory	**CNS Outcome:** Cerebral palsy **Ophthalmology:** Visual impairment **Audiology:** Deafness **Growth:** Height Weight Head circumference	CP: spastic diplegia, spastic hemiplegia, spastic hemiplegia Scheffzek's categories of functional disabilities are not defined in this article. They refer to a previous article which is written in German. "Major Handicaps" (category 3-4) CP, severe visual impairment, CP+ severe visual impairment, mental retardation and cardiomyopathy, hearing less
Gregoire 1998 98232532	Cardiovascular/Pulmonary: 1) Chronic Lung Disease 2) Bronchopulmonary dysplasia Compared O_2 dependence at 28 days with O_2 dependence at 36 wk	ND	**CNS:** Cerebral palsy Motor and cognitive delay **Audiology**: Hearing Disorders→ Free field audiograms **Pulmonary:** Respiratory readmissions PICU admissions **Growth:** Weight, height, head circumference **Other:** Health Outcomes	Giffith's Mental Development Scales Neurologic examinations

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Kurkinen-Raty 1998 98387235 (All+Lung) ***sample from the same big population as 20284814**	General : PROM	Diagnose was through clinical assessment or with the use of a PROM-test, which detects insulin growth factor binding protein-1 in the cervico-vaginal secretions, or with the use of a nitrazine test.	**CNS:** Motor delay Cerebral delay **Ophthalmology**: Visual Blindness **Audiology:** Hearing disorders **Pulmonary**: Chronic lung disease **Growth:** weight percent **Other:** Days of re-hospitalization Steroid therapy at followed up	Neurologic exams Diagnosis of CLD was made if infants required oxygen, continuous bronchodilator, or steroid tx because of respiratory signs and symptoms. Diagnoses of RDS were made based on need for respiratory support, radiologic findings, and clinical assessments

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Lee 1998 98442293	**General:** 1) Candidemia and/or Candidal meningitis	Diagnosis of Candidemia: by at least one positive Blood Culture Diagnosis of Candidal meningitis: by isolation of Candida in the CSF or >45x10 ^{6} WBCs in the CSF and candidemia.	**CNS:** Neurodevelopmental disabilities (NDDs) Cognitive delay Cerebral palsy **Ophthalmology:** Legal blindness **Audiology:** Hearing loss **Growth:** Growth retardation	1) Bayley Scales of Infant development; MDI, PDI for ages < 24 mo. 2) Stanford-Binet Intelligence Scale and Peabody Development Motor Scales for ages > 24 mo 3) Scores obtained by psychologists, psychometricians, pediatricians specialized. Neurodevelopmental Disabilities: 1) Cerebral palsy (all types and severity) 2) Legal blindness (corrected VA of the better eye<20/200) 3) Hearing loss (neurosensory hearing loss in the better ear > 30 dB) (done by certified audiologist 4) And/or cognitive delay (MDI>3 SDs below the mean) Growth retardation: Weight, Height, HC > 2 SDs below the mean (Between 3-6 yrs CA)

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Lefebvre 1998 98387703	Other: Neurobiologic risk score (NBRS)	Items in NBRS: ventilation, PH, surgeries, IVH< PVL, infection, hypoglycemia-items scored zero or greater in progression	**CNS:** Cerebral palsy Cognitive delay Other neurodevelopmental impairment **Ophthalmology**: Blindness **Audiology:** hearing disorders-free fetal audiogram	Neurologic exam Griffith's mental development scale Mental retardation-Griffith's mental development scale 1) Global developmental quotient (DA) 2) Mild/moderate: DA 80-89 or CP 3) Severe: DA<80, severe CP unilateral blindness or severe hearing defect 4) Normal: more of the above Areas of Griffith's Developmental Scales: - Locomotor - Personal-social - Hearing and speech - Eye and hand coordination - Performance Control mean DA=110+or- in literature
Millet 1998 98212544	CNS: MRI findings at 3-6 months	ND	**CNS:** Motor delay Cerebral palsy Cognitive delay Behavioral disorders **Ophthalmology:** Visual impairment **Audiology:** Hearing loss **GI:** Dysphagia	Neurodevelopmental outcome poorly defined

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Piecuch 1998 98446413	**General:** 1) Birth in a recent period vs early period vs midpoint period (the authors wanted to assess whether changes in neonatology for the care of VLBW infants have changed the outcome of LBW infants: 1000-1500g) 2) Birth weight 3) GA 4) Gender 5) Place of birth (inborn vs outborn) 6) Weight for age (AGA vs SGA) **CNS:** 1) Intracranial hemorrhage (ICH) **Pulmonary:** 1) Duration of mechanical ventilation 2) Duration of O2 requirements (CLD)	Birth in a recent period: 1989-1991 Birth in an early period : 1979-1981 Birth in a midpoint period:1984-1986	**CNS:** 1) Neurologic: normal, suspect, abnormal 2) Cognitive: Average or above, Mild delays, Moderate/severe delays **Ophthalmology-Audiology:** Significant visual and/ or auditory deficits (B/L blindness or need for hearing aids)	Neurologic: 1) Normal 2) Suspect: (clumsiness, tremors, mild tone and reflexes changes, but without fixed impairment) 3) Abnormal: moderate/ severe: fixed impairments such as CP, diplegias, hemiplegias Sensory 1) Visual acuity screening 2) Behavioral screening assessment Cognitive: < 24 mo: Bayley Scale >24 mo: Stanford-Binet scale Carthy Scale 7-8 yrs: Wechsler Intelligence Scale for Children Revised 1) Average or above 2) Mild delays: 1-2 SDs below mean 3) Moderate/severe delays: > 2 SDs below mean Time of outcome assessment not specified: It could be done up to age 7.5-8 yrs (Mean age at assessment in the cohort was: 24 mo)

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Sajaniemi 1998 99041674	General: 1) Prematurity per se 2) Premature with BW< 1000 g vs premature with BW > 1000 g 3) Pre-eclampsia 4) SGA 5) Duration of NICU stay **CNS:** 1) PVL 2) IVH **Pulmonary:** 1) Duration of ventilation	Not further specified	**CNS:** Neurologic outcome Developmental outcome Temperament profile Behavioral profile	Neurologic outcome: 1) Cerebral palsy 2) Free of major disabilities Developmental outcome: 1) Bayley Scales of Infant Development 2) Mental Development Index (MDI) Temperament: Toddler Temperament questionnaire (TTQ) (contains 97 statements) 9 temperament dimensions: 1) Activity 2) Rhythmicity 3) Approach 4) Adaptability 5) Intensity 6) Mood Persistence 7) Distractability 8) Threshold Behavior: Infant Behavior Record: 1) Social responsiveness 2) Attention 3) Affect 4) Energy level 5) Goal directedness during the test (24 mo CA)

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Scherjon 1998 98429216	**CNS:** 1) U/C ratio: Doppler finding of umbilical/cerebral artery pulsatility index (U/C ratio: raised vs normal) 2) Neonatal Cranial Ultrasound findings **General:** 1) Fetal growth ratio 2) GA	1) U/C ratio: The ratio between umbilical artery and cerebral artery pulsatility index (used as a marker of fetal blood redistribution to the brain, and indirect marker of placental insufficiency) 2) Neonatal cranial Ultrasound: Normal: No intracranial or subependymal bleeding, Echodensities less bright than choroid plexus Moderate: IVH (< 50% of lumen filled) some echodensity brighter than choroid plexus, lasting less than 3 days. Abnormal: IVH (>50% of lumen filled) Intraparenchymal bleeding Some echodensities brighter than choroid plexus and lasting longer than 3 days 3) Fetal growth ratio (observed birth weight divided by expected mean BW for GA)	**Growth:** Growth (Weight, Height, HC) **CNS:** Neurodevelopmental outcome Behavioral outcome	Hempel outcome: 1) Specific for toddlers 2) Observed children while playing in a standardized situation 3) 89 items Motor aspects of Hempel examination: Classification of infants: 1) Normal 2) Mildly abnormal (e.g., slight asymmetry, or mild hypo-, hyper-tonia which does not lead to handicapping condition) 3) Abnormal (e.g., CP, which leads to handicap in daily life) Behavioral aspects of Hempel examination: 1) Information based on parental questionnaire on child's cognitive function and 2) language skills (level of activity, nocturnal enuresis, eating, sleeping disturbances, language development, comprehensibility, passive understanding, number of words used in sentences) Hempel outcome assessment was done by a person blind to prior medical history of child. (3 yrs CA)

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Cheung 1999 99146391	*General predictors:* 1) BW 2) GA 3) Apgar score *CNS predictors:* 1) intracranial/ intraventricular hemorrhage *Cardiovascular or pulmonary predictors:* 1) days of ventilation 2) days of O_2 use *Other predictors:* 1) frequency of apnea 2) mean desaturation of apnea 3) mean frequency of apnea 4) Blisten index (socioeconomic status)	ND	**CNS outcomes:** Motor delay Cerebral palsy Cognitive delay Mental retardation Seizure disorder Neurodevelopmental disability **Ophthalmology outcomes:** Blindness **Audiology outcomes:** Hearing disorders **Growth outcomes:** Weight > 2 SD below the mean Height > 2 SD below the mean HC > 2 SD below the mean	Bayley scores Stanford-Binet Intelligence Scale Peabody Developmental Motor Scale Neurodevelopmental disability: "children with 1 or more of a) cerebral palsy b) legal blindness c) hearing loss d) convulsive disorder e) cognitive delay
Duvanel 1999 99207097	**General:** 1) Hypoglycemia: 2) Severity of hypoglycemia (0-11 mg/dl, 11-29 mg/dl, 29-47 mg/dl), and 3) Frequencies of hypoglycemic episodes	Blood glucose level in the first 24 hours of less than 47 mg/dl by reagents sticks, or confirmed by glucose analyzer for stick measurements less than 36mg/dl. About the frequency of episodes: no Precise information on the frequency Of performance of glucose measurements.	**CNS:** Scores in psychometric tests done for neurodevelopmental assessment at: ➢ 6 moths ➢ 12 moths ➢ 18 months ➢ 3.5 yrs ➢ 5 yrs. **Growth:** Head circumference at ➢ 6, 12, 18 months, 3.5 yrs, 5 yrs ➢ Growth rates for weight, length, and HC for time intervals: ➢ 6-18 months ➢ 6-3.5 yrs ➢ 6-5 yrs	Griffith's test (6 items): at 6, 12, 18 mo McCarthy test (6 items) : 3.5 yrs, 5 yrs

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Pennefather, 1999 20002011 Pennefather, 2000 20217908 *** This study is also in eye table**	*Genera Predictor:* GA CNS: 1) IVH 2) Periventricular leukomalacia 3) Ventriculomegaly/Ventricular Dilation Ophthalmology: 1) ROP 2) Refractive error Other: Family Hxg strabismus, Developmental disability, CP	ND	**CNS:** Cerebral palsy **Ophthalmology:** Visual impairment (cortical)(CVI) Cicatricial ROP Strabismus	Retrospective review of patient records Visual acuity, Visual fields
Ambalavanan 2000 21031370	General: BW, GA, Antenatal steroids, Apgar score Other: Race, Gender Multiple gestation, Maternal education, Maternal age CNS: Intracranial hemorrhage Periventricular/Ventricular Dilation Bronchopulmonary dysplasia GI: Necrotizing "entrocolitis" Interinal perforation, Chorioamnionitis Multiple gestation Maternal education Maternal age	Extensive list of the 21 predictor variables	**CNS:** Motor delay Cerebral palsy Cognitive delay Mental retardation PHH Neurologic exam Major handicap **Ophthalmology:** Visual impairment Blindness **Audiology:** Hearing disorders Deafness	Bayley Scales of Infant Development Major handicap-presence of one or any poor outcome (i.e. CP, deadness, blindness). Mental retardation (MDI or PDI <70), PHH requiring sheet

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Cioni 2000 20150341	CNS intracranial hemorrhages, white matter disorder, Ventriculomegaly	MRI findings Total MRI score (the higher the worse, range 7-21) made by summation of subscores of following categories: Size of Lateral ventricles, white matter abnormal signal intensity, white matter reduction, cysts, size of subarachnoid space, corpus callosum, cortical gray matter; MRI score of visual cortex and optic radiations	**CNS:** CP **Ophthalmology:** Visual assessment **Developmental**	**Neurological examination:** Normal Mildly abnormal (mild retardation and/or mild abnormal neurological signs, but not CP. CP with relatively normal head and trunk control. CP without head and trunk control. **<u>Visual assessment:</u>** Grating acuity: assessed with binocular Teller acuity card procedure (cycles per second) Visual Field (kinetic perimetry) Horizontal optokinetic nystagmus (OKN) Oculomotor behaviour (following and fixation) and strabismus. **<u>Developmental Assessment:</u>** Griffith's developmental scales (global and each subscale: locomotor, personal-social, hearing-speech, hand-eye co-ordination, and performance) Scores ≥85 = normal Borderline 84-71 Abnormal ≤70

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Hack 2000 20358826	General: 1) Birth weight 2)GA 3) SGA/IUGR 4) Antenatal steroids 5) Jaundice CNS: 1) Intracranial/Intraventricular Hemorrhage 2) Periventricular leukomalacia 3) Ventriculomegaly/ ventricular dilation Cardiovascular/Pulmonary: Chronic lung disease Gastrointestinal: Necrotizing "entroclitis" Other: 1) Infectious Disease 2) Dexamethasone 3) Perinatal factors (chorioamnionotis) 4) Multiple birth 5) C-section 6) Social risk 7) Male sex	ND	**CNS:** Cerebral palsy Motor delay Cognitive delay MDI score<70 Post hemorrhagic Hydrocephalus **Ophthalmology**: Blindness **Audiology:** Deafness	Neurologic abnormality - includes: CP, hypotonia, hypertonia Shunt-dependent hydrocephalus
Jankov 2000 20188680	Cardiovascular predictors: 1) CPR Other predictors: 1) Apgar scores	1) 2) Use of CPR in delivery room 3) Assignment of Apgar scores in the delivery room	**CNS outcomes:** Cerebral palsy Cognitive delay Mental retardation Adverse outcome **Ophthalmology outcome:** Blindness **Audiology outcome:** Hearing disorders	Adverse outcome defined as: 1) CP causing non-ambulation beyond 2 years or spastic quadriparesis 2) Intellectual delay = below 2 SD 3) Hearing loss requiring aids 4) Legal blindness (<20/200)

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Kurkinen-Raty, 2000 20284814 ***sample from the same big population as 98197235**	General predictors: Birth weight GA Antenatal steroids Cord pH Bronchopulmonary dysphasia (BPD) Other predictors: Indicated preterm delivery Spontaneous preterm delivery	BPD diagnoses were based on radiologic finding	**CNS:** Motor delay Cerebral palsy **Ophthalmology** Visual impairment **Audiology** Hearing disorder **Pulmonary** Chronic lung disease (CLD) at 1 year **Growth:** *Wt, Ht, HC*	Motor delay = abnormalities of tone or reflexes but functionally normal or borderline CP = spastic diplegia or hemiplegia or spastictetraplegia Diagnosis of CLD was made if infants required oxygen, continuous bronchodilator, or steroid tx because of respiratory signs and symptoms.

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Marlow 2000 20150342	**General:** 1) Birth weight 2) Apgar score 3) CRIB scores **CNS:** 1) Maximum bilirubin level 2) Abnormal cerebral US scan **Audiology:** 1) Sensorineural hearing loss **Cardiovascular/Pulomonary:** 1) Duration of intubation, respiratory support, oxygen, pH<7.2, base excess 2) Dopamine excess 3) Furosemide 4) Indomethacin use **Other:** 3) Netilmicin 6) Vancomycin 7) Positive blood cultures 8) Bilirubin >200 ?mol/l 9) Bilirubin>GA x 10 10) Creatinine >60 mmol/l 11) Netilmicin 12) Vancomycin Combination of the above: 1) Bili.200 + acidosis 2) Bili> 200 + sepsis 3) Bili >200+ netilmicin 4) Bili> 200+ vancomycin 5) Bili>200+ furosemide 6) Peak bil+ acidosis 7) Peak bili+ sepsis 8) Peak bili+ netilmicin 9) Peak bili+ furosemide 10) Creatinine>60+ netilmicin or vancomycin or furosemide 11) Netilmicin+furosemide 12) Vancomycin+ furosemide	Not further specified	In case control component: **Audiology:** Sensorineural hearing loss (SNHL) of 50 dB within 9 months from birth In Longitudinal component: **CNS:** Cerebral palsy at 12 months of age in the 2 groups (SNHL and control group)	Cases of SNHL were identified if the hearing loss had been identified within 3 months of discharge home, (within 9 mo from birth); after excluding cases with conductive hearing loss, possible congenital cause, or had neonatal bacterial meningitis

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Victorian Infant Collaborative study Group, 2000 20307288 ***some subjects were overlapped with Doyle, 2001**	Other: Dexamethasone-Postnatal	ND	**CNS:** Cerebral palsy Cognitive delay **Ophthalmology:** Blindness **Audiology:** Deafness	Wechsler PPSI-R
Wood 2000 20373840	*General:* 1) GA 2) Gender Other: Perinatal Factors→ Multiple gestation	ND	**CNS:** Motor delay Cognitive delay Seizure disorder Overall development **Ophthalmology:** Visual impairment Blindness **Audiology:** Hearing disorders Deafness Speech Communication disorder **Other:** Severely disabled Other disability No disability Disability of hearing, vision, or communication	Bayley scales Severe disability = need of physical assistance to perform daily activities. If disability did not fit into this category = "other disability"

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Doyle 2001 21326609 Victorian Infant Collaborative study Group, 1997 97290716 ***some subjects were overlapped with 20307288 (stated in text)** ***possibly overlapped with 98026322**	*General predictors:* 1) GA 2) SGA/IUGR 3) antenatal steroids 4) gender (female) 5) postnatal age *CNS predictors:* 1) intracranial/ intraventricular hemorrhage 2) periventricular leukomalacia *Cardiovascular or pulmonary predictors:* 1) bronchopulmonary dysplasia *Other predictors:* 1) dexamethasone 2) perinatal factors a) multiple birth b) cesarian section 3) socioeconomic variables i) Asian mother ii) higher SEC iii) no English-speaking at home 4) surgery in primary hospital 5) patient with no adverse events	1) SGA/IUGR - BW ratio <0.8 2) intracranial/ intraventricular hemorrhage - Papille system 3) periventricular leukomalacia - cystic lesions in PVWM dx < discharge 4) bronchopulmonary dysplasia - ROS + O_2 Rx after 28 days age 5) dexamethasone - postnatal steroid use	**CNS:** Motor delay Cerebral palsy Cognitive delay Mental retardation **Ophthalmology outcomes** Blindness **Audiology outcomes:** Hearing disorders Deafness **Other outcomes:** Survival without major disability at 5 years age Survival with major neurosensory disability at 5 years age	1) motor delay, cognitive delay - WPPSI-R and alternative IQ tests 2) cerebral palsy - not walking or walking with difficulty 3) mental retardation - IQ < 2 SD below mean for NBW group

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Gaillard 2001 21221175	In retrospective case-control component: **General:** 1) shorter length of ventilation beyond 27 (but not 50) postnatal ds vs more prolonged ventilation beyond 49 ds 2) Number of days "off"" ventilator in the groups of 27-49 postnatal ds ventilation and the group of >49ds ventilation In retrospective cohort with historical control group component: **GeneraL:** 1) Birth in a period where Antenatal steroids and Surfactant were more routinely used vs birth in pre-surfactant pre-antenatal steroid period	Not further specified	**CNS:** Neurodevelopmental outcome: 1) Normal 2) Mild disability 3) Moderate disability 4) Severe disability	Normal neurodevelopmentally: no clinically apparent neurodevelopmental abnormality causing functional disability Mild disability: e.g. myopia, language delay, mild hearing loss, hyperactivity or motor clumsiness. Moderate disability: for example: spastic diplegia, hemiplegia or moderate learning disability (Developmental Quotient: 50-69) Severe disability: e.g. spastic quadriplegia, blindness, deafness (loss of 70 decibel or more), uncontrolled epilepsy, or severe learning disability (developmental quotient <50). Infants with multiple disabilities. (3 yrs CA)

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Roth 2001 21262686	CNS: 1) intracranial/Intraventricular hemorrhage 2) white matter disorder 3) Periventricular leukomalacia 4) Ventriculomegaly/ventricular dilation 5) Ultrasound methodology: linear array vs mechanical sector	ND	**CNS:** Motor delay Cerebral palsy Cognitive delay Mental retardation School problems Learning disabilities **Ophthalmology:** Visual impairment Blindness **Audiology:** Hearing disorder Deafness	Outcome categories: 1) No neurodevelopmental impairment 2) Detectable impairment with disability (included neuromotor impairment with functional consequences, high tore hearing loss with need for aid, IQ 70-79, informal "help" in mainstream school) 3) Impairment leading to disability (included neuromotor impairment leading to disability sensory neural hearing loss, requiring aids, blindness or registered partial sight, IQ<70 or requirement for formal extra educational provision
Saigal 2001 21376729 *** Important paper**	Birth weight GA	ELBW=500-1000 g	**CNS:** Motor delay Cognitive delay Other: neurosensory impairment **Ophthalmology:** Visual impairment **Growth:** 1) height 2) weight 3) head circumferences 4) BMI (wt/ht2) **Other:** 1) Health status and problems ; current and past 2) Extra health care expenses 3) Utilization and health care resources	Reported previously in the authors' other paper Growth reference population was using the age- and gender- specific reference data provided by the NCHS growth chart

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Schmidt 2001 21298249	1) Prophylactic indomethacin administration : 0.1 mg/kg Q24 hrs X 3 days (vs NS placebo) in VLBW infants, during first 6 hrs of life	Nor further specified	Primary outcomes at 18 months of age: 1) Composite outcome: death or impairment 2) Death before 18 mo corrected age 3) Cerebral palsy 4) Cognitive delay (MDI<70) 5) Hearing loss requiring amplification 6) Bilateral blindness Secondary long term outcomes outcomes: 1) Hydrocephalus, necessitating the placement of shunt 2) Seizure disorders 3) Microcephaly (HC<3 d %)	1) Death before a corrected age of 18 months or documentation in survivors of one of the following: CP, Cognitive delay, Hearing loss requiring amplification, B/L blindness 2) Cerebral palsy diagnosed if had nonprogressive motor impairment with abnormal muscle tone and decreased range or control of movements. 3) Cognitive delay: as MDI less than 70 (2SD below the mean of 100) on the Bayley scale between 85-114: classified as normal, Scores below 70: marked cognitive delay. 4) Documentation of composite primary outcome: required documentation that the infant had died or had survived with one of the 4 types of impairment. A single missing component of the f/up assessment would result in designation of missing for primary outcome. A priori criteria for definitions of presence or absence of component of the primary outcome. 5) In cases it was difficult to obtain Audiologic test results, deafness requiring amplification was assumed to be absent if no such indication was present during the Bayley test. (n=27) 6) Blindness: a corrected visual Acuity of less than 20/200. F/up evaluation around 18 mo: allowed range 18-21 mo. (Home visits were permitted when necessary)

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part III

Author, Year	Associations found	Potential Biases	Comments
Akerman 1992 93255928	Physical and Emotional Problems at 4yrs: Psychomotor retardation-------- 11.8% Impaired hearing----------2.9% Impaired vision----------2.9% Delay in speech/language--------11.8% Emotional Problems----------2.9% No physical or psychological problems----------67.7% All except 3 infants with physical and emotional problems were either premature or weighed less than 2500 gms at birth. Of the 22 infants with physical or psychomotor impairment, 17 were males	No infant weighed less than 1250 g Population homogeneous middle class with access to medical care	No data on funding source
Thompson 1993 93234177	Two years CA neurodevelopmental outcome and Griffith's scores for a cohort of South African infants with BW < 1250 g, n = 96. Mechanical ventilation not routinely used when BW < 900g. Percent with outcome Normal 75% CP 6% DQ < 70 and CP 3% DQ < 70, no CP 1% DQ 70-79 and CP 0 DQ 70-79, no CP 15% Hyperactive 3% "Squint" 0 Developmental delay 0 Scores on Griffith'sscales for most items fell significantly (P < 0.001) between one and two years of CA. Overall major handicap rate rose between years 1 and 2 CA from 14% to 22%	(None)	Study was private funded

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year	Associations found	Potential Biases	Comments
Rademaker 1994 95003452	3.6% of the Preemie population (= 32 weeks) have unilateral intracranial parenchymal lesion. Not all unilateral parenchymal lesions are the same. Size of the lesion, location of the lesion, and whether the lesion communicates with the ventricle at any time all have important role in prediction of neurodevelopmental outcome. For example, if the initial lesion is triangular/fan-shaped and does not communicate with the ventricle at any time and is located in the fronto-parietal area, overall prognosis is favorable. But if the lesion is globular-shaped, continuous with the ventricle and extends beyond the trigone into the occipital periventricular white matter, risk for death and developing moderate to severe hemiplegia is significantly increased.	Small sample size	No data on funding source Cases series

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year	Associations found	Potential Biases	Comments
Vonderveid 1994 94297368	Of all these 22 predictors/variables evaluated for **CNS** outcomes : • PVL was associated with more than 5-fold increase in the risk of **CP** (OR: 5.8; 95% CI: 3.8-8.8) • Acidosis during hospitalization was associated with more than 1.5-fold increase in the risk of CP (OR: 1.6; 95% CI: 1.1-2.4) Overall in this NICU cohort: there were: 443/634 (70%) LBW and 191/634 (30%) were VLBW Overall **CNS outcomes** at 2 yrs: 1) Functionally normal were: • 52% of all prematures • 25% of VLBWs • 63% of LBWs 2) 62/634 (10%) children had one or more disabilities • 46/62 (74%) had CP of severity score 2-4 • 2 had peripheral motor disability • 9 had DQ< 80 (without motor or sensory disability) **Ophthalmology outcome:** 1) 8 were blind due to ROP (3 also had CP) **Audiology outcome:** 1) 1 was deaf (was also blind and had CP) A definite handicap was considered for: • 21/62 (34%) disabled children • (21/634=3%) (according to WHO definitions)	• Cannot exclude Diagnosis bias as no information is given on blinding of personnel doing the outcome assessment on PMHx of the child. • Cannot exclude false Association found due to high number of predictors analyzed for the number of CP events (22 predictors for 46 CP cases)	

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part III

Author, Year	Associations found	Potential Biases	Comments
Kraybill 1995 95264242	Predictor evaluation for **Pulmonary, Growth and Neurodevelopmental outcomes at 1 yr.** Single dose Surfactant tx at birth was not associated with the pulmonary, growth, neurodevelopmental and neurosensory status of VLBW premature infants at 1 yr of corrected age *Placebo group vs Surfactant group, at 1 yr of age:* 1) Overall survival at 1 yr: 160/193 (83%) vs 163/192 (85%) **Pulmonary:** 1) Oxygen via NC: 4/122 (3%) vs 2/136 (1.5%) 2) Oxygen via CPAP: 0/122 vs 1/136 3) CLD: 8/122 (6.5%) vs 10/136 (7%) **Growth:** 1) Distribution of pts in both groups across different percentiles: Ht/age, Weight/age and HC/age: were not s/s different across the two groups. **CNS:** 1) Mean MDI score: 85 ± 20 vs 88 ±22 (not ss)) 2) MDI scores< 2SDs : 11/118 vs 23/133 3) Mean PDI score: 89±22 vs 91 ±23 (not ss) 4) PDI scores < 2 SDs: 11/118 vs 8/133 5) No impairment: 69/119 (58%) vs 78/134 (58%) 6) Impairment present (total): 50/119 (42%) vs 56/134 (42%) 7) Severe impairment: 29/119 (24%) vs 37/ 134 (28%) 8) Mild/Moderate impairment: 21/119 (18%) vs 19/134 (14%) 9) Types of impairment: MDI<69: 21/119 (18%) vs 27/134 (20%) MDI: 69-84: 19/119 (16%) vs 20/134 (15%) Moderate/severe CP: 10/119 (8%) vs 9/134 (7%) Mild CP: 10/119 (8%) vs 12/ 134 (9%) **Audiology:** 1) Bilateral sensorineural deafness: 0% vs 0% 2) Deafness not requiring amplification 1/119 (1%) vs 2/134 (1%) **Ophthalmology:** 1) Bilateral blindness: 4/119 (3%) vs 2/134 (1%) 2) Visual defect: 9/119 (8%) vs 9/134 (7%) Assessment from 28ds-12 mo:		

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year	Associations found	Potential Biases	Comments
Kraybill 1995 95264242 (continued)	• No ROP: 50/132 (38%) vs 57/143 (40%) • Present ROP overall: 82/132 (62%) vs 86/143 (60%) • Mild/Moderate ROP: 79/132 (60%) vs 84/143 (59%) • Severe ROP: 3/132 (5%) vs 2/143 (2%) • Treatment for ROP overall: 7/132 (5%) vs 10/ 143 (7%) Surgery: 4/132 (3%) vs 3/143 (2%) Cryotherapy: 4/132 (3%) vs 8/143 (6%) In the NCMH cohort there was no difference in impairments (present or absent), the severity of impairments and the types of impairments at the 1yr of age assessment of this cohort) Predictor evaluation for **Pulmonary, Growth and Neurodevelopmental outcomes at 2 yr.** Single dose of Surfactant tx at birth was not associated with the pulmonary, growth, neurodevelopmental and neurosensory status of VLBW premature infants at 2 yrs of corrected age24/52 (46%) *Placebo group vs Surfactant group, at 2 yr of age:* • Overall survival at NCMH only at 2 yrs: 68/60 (13%) vs 67/83 (81%) **Pulmonary:** 1) Hospitalized for respiratory illness: 9/84 (82%) vs 9/52 (17%) 2) Bronchodilator regular use: 10/61 (16%) vs 6/57 (11%) 3) Tracheostomy: 2/61 (3%) vs 0/57 **Growth:** 1) Distribution of pts in both groups across different percentiles: Ht/age, Weight/age and HC/age were: not s/s different across the two groups **CNS:** 1) Mean MDI score: 89 ±21 vs 90 ±19 2) MDI scores< 2SDs: 5/58 (9%) vs 2/48 (4%) (NS) 3) Mean PDI score: 89 ±18 vs 88 ±16 4) PDI scores < 2 SDs: 4/58 (8%) vs 3/48 (7%) 5) No impairment: 32/60 (53%) vs 24/52 (46%) 6) Impairment present (total): 28/60 (47%) vs 28/52 (54%) (NS) 7) Severe impairment: 11/60 (18%) vs 7/52 (13%) 8) Mild/Moderate impairment: 17/60 (28%) vs 21/52 (40%)		

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year	Associations found	Potential Biases	Comments
Kraybill 1995 95264242 Continued	9) Types of impairment: MDI<69: 8/60 (13%) vs 2/52 (4%) MDI: 69-84: 14/60 (23%) vs 18/52 (35%) (NS) Moderate/severe CP: 6/60 (10%) vs 5/52 (10%) (NS) Mild CP: 2/60 (3%) vs 3/52 (6%) (NS) **Audiology:** 1) Bilateral sensorineural deafness: 0 vs 0 2) Deafness not requiring amplification: 0 vs 0 **Ophthalmology:** 1) Bilateral blindness: 0 vs 3/52 (6%) 2) Visual defect: 8/60 (13%) vs 2/52 (4%) (not ss) **Others:** 1) Any surgery (between 1-2 yrs): 10% vs 9 % Administration of single dose surfactant at birth in premature VLBW infants, with BW: 700-1350 g, results in improved survival rates up to 28 ds, without BPD and is not associated with adverse physical or neurodevelopmental outcomes at 1 yr or 2 yr corrected age.		

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Author, Year	Associations found	Potential Biases	Comments
Speechley 1995 96356544	**General Health outcome:** Among boys around 12 yrs of age: NICU graduates as opposed to normal boys: 1) Are living with more chronic health problems 2) Are more likely to have a physical impairment 3) And have been hospitalized more often. Among girls around 12 yrs of age: NICU graduates as compared to normal girls: No statistically significant differences in their physical health outcome. Among NICU graduates, boys were not different from girls in their long-term physical health outcomes. **Emotional and Social well being outcomes:** Among girls around 12 yrs of age: NICU graduates as opposed to normal girls: 1) Had significantly lower social competence 2) Lower social support 3) And Lower self-esteem. Among boys around 12 yrs of age: NICU graduates as compared to normal boys: 1) They had no difference in their emotional or social well being. There was no interaction between family's socioeconomic status and long term outcomes among NICU graduates. Analytically: The **physical health outcomes** at 12 yrs were (**Boys NICU** grads vs Boys NNN grads/ **Girls NICU** grads vs Girls NNN grads) • Chronic physical health (mother's report): 2.8 vs 1.8 (p<0.005)/ 2.4 vs 1.3 • Lifetime hospitalizations (mother's report): 2.5 vs 1.6 (p<0.005)/ 1.7 vs 0.4 • Physical impairments (mother's report): 0.29 vs 0.10 (p<0.005)/ 0.22 vs 0.06 • Perception of child's heath (child's report): 21.6 vs 22.2/ 21.1 vs 21.9 • Perception of child's health (mother's report): 16.9 vs 17.7/ 16.8vs 18.0 **Emotional and social well being at 12 yrs:** (Boys NICU grads vs Boys NNN grads, Girls NICU grads vs Girls NNN grads) • Internalizing problems (child's report):15.3 vs 15.5/ 18.2 vs 14.8 • Externalizing problems (child's report): 15.9 vs 16.0 / 14.3 vs 13.5 • Social competence (child's report): 109.1 vs 113.9 / 101.7 vs 115.7 (p<0.005 • Social support (child's report): 81.6 vs 83.2/ 79.9 vs 86.1 (p<0.005) • Self esteem (child's report): 31.9 vs 32.4/ 29.8 vs 32.5 (p<0.005) • School performance (mother's report): 4.5 vs 4.6/ 4.8 vs 5.3	1) There is an inconsistency in mother's appreciation of their child's physical health: mothers of NICU graduate boys reported that their children had more physical impairments than NNN boy graduates; however, their overall perception of their child's health status was not any different from NNN boys graduates. 2) Some of the outcomes collected are prone to recollection bias (e.g., frequency of lifetime hospitalizations).	1) In this NICU cohort, only 36% of infants had BW<2500 g and only 5% had BW < 1500 gs, reflecting more NICU populations in the 1970s and early 1980s than the current ones. 2) It is unclear whether statistically significant differences in psychometric scales, with 10-36 items each, reflect clinically significant differences in the emotional and social well wellbeing of these children. 3) Conversely, given the fact of many negative findings, post hoc power analyses demonstrated that the study had an 80% power to detect a 40% difference between the 2 groups. (considering 20% as small effect and 50% as medium effect) 4) The fact that girl NICU graduates had a more substantial psychological effect than boys may reflect that girls are further into adolescence than the boys, experiencing the sequelae earlier. Thus in order to determine whether the differences observed are a temporary effect/related to adolescence, this cohort had to be followed further into their teenage years

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Author, Year	Associations found	Potential Biases	Comments
Hack 1996 97060805	At 8 year age, 10% of VLBW (24/249) had major neurosensory abnormality vs. 0% of Normal Birth Weight. At 8 years age, VLBW vs. Normal Birth weight were significantly less for each of the growth outcomes: weight, height, and head circumference ($p<0.001$) Significantly greater % of former VLBW infants with (22%) vs. without (7%) major neurosensory abnormal had significantly greater subnormal growth at 8 yr (OR 3.91, 95% CI 1.18-12.88). VLBW with major neurosensory abnormal had no catch-up growth after 20 months age. VLBW +SGA had increased odds of subnormal growth at 8 years (OR 3.89, 95%CI 1.35-11.23)	(None)	No data on funding source ELBW: Lost to follow-up (22), families refused (17), families moved out of state (20)
Hack 1996 97066007	MR (MDI<84) / CP / Blind / Deaf / Major Neurosensory abnormal +MDI<80 1982-1988: 52% / 10% / 10% / - / 49% 1990-1992: 34% / 10% / 2% / 6% / 35% 20-month Neurodevelopmental outcomes did not change appreciably between the 2 eras. 20% of infants had subnormal cognitive function (MDI<70) and 10% had CP during 1990-1992 period. One third of infants with BW 500-750 gram had major neurosensory abnormalities and / or MDI<80.	(None)	No data on funding source
Northern Neonatal Nursing Initative Trial Group 1996 96304894	No significant differences by Griffith's Developmental quotients, incidence of CP, seizures, hearing disorders. Initial demographics available in an earlier study.	(None)	Study was government and privately funded

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year	Associations found	Potential Biases	Comments
Sethi 1996 96334245	Single evaluation at 2 years age. Follow-up information available for 99% of cohort. Normal 70% Major impairment 11% Minor impairment 19% Cerebral palsy 8.7% Blindness 2%	Results are from a single district general hospital No accounting for confounders: IVH, antenatal steroids, etc. Very little information provided to characterize groups BW distribution, degree of illness, IVH, BPD, etc. Inadequate information about population and about determination of cognitive function	No data on funding source 93 infants; follow-up available for 92; 20 infants had follow-up data from local medical care center rather than clinic visits
Wilkinson 1996 97087405	Among 10 surviving infants GA<35 wk/ BW<1500 gm who had severe cystic PVL, all (100%) had severe neurodevelopmental outcome (CNS [spastic quadriplegia, abnl neuro exam, seizures], impaired vision and hearing) at mean 27.3 mo age.	10/12 examined (8 by single neurologist/ 2 by pediatrician and neurologist) 9/10 eye examined in NICU ? 7/10 followed as outpatients Not a complete population sample of all GA<35 weeks or BW<1500 g with complete scanning data Small sample size	No data on funding source

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year	Associations found	Potential Biases	Comments
DeReginer 1997 98041177	**Chronic lung disease** Any adverse outcome: 2/54 12/54 P<0.001 18/56 Sensorineural hearing loss: 0/54 0/54 P<0.05 3/56 Low MDI<2 SD from mean: 0/54 4/54 P<0.05 5/56 Low PDI<2 SD from mean: 1/54 4/54 P<0.05 7/56 Weight Z-score: No numbers given <0.05 Chronic lung disease and cerebral palsy, unilateral blindness, length Z-score, head circumference Z-score are not significant.	Matching scheme used is likely to be ineffective Large proportion of study population excluded by their matching strategy: subjects excluded were: 329/387=85% with no chronic lung disease; 53/111=47.7% with mild chronic lung disease; 122/180=68% with severe chronic lung disease	No data on funding source
Dezoete 1997 97359687	Outcome of category I & II: SGA: No difference between SGA and AGA infants IVA gr. III, IV: signify more cat I & II outcome with gr III-IV IVA vs I+II P= 0.01 Category IV: CLD: Children with CLD more likely to be normal (category IV) P<0.01	Entry criteria of infants that admitted to NICU; don't know standards of resuscitation in all 276 centers and it expertise of resuscitators creates a different kind of population.	No data on funding source

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Author, Year	Associations found	Potential Biases	Comments
O'Shea 1997 98049056 ***overlapped sample with 98190123**	*Major neurosensory impairment:* Grade 3 LVH or PVE: 6.21(2.56, 15.101) *CP:* Total: (N=216) 14% (17/129 survivors) *Blindness:* Total: (N=126) 4% (5/129 survivors) *MDI<68* Total: (N=216) 14% (17/129 survivors)	(None)	Study was government funded
Piecuch 1997 97456215	Neurologic abnormal, neurosensory abnormal, cognitive abnormal BW No association Neurologic: GA Negative association Neurologic/neurosensory: ICH/PVL Significant association with abnormal outcome Cognitive: CLD Significant association with poor outcome Social risk Strong association No association was found between outcome and birth weight.	(None)	No data on funding source
Piecuch 1997 98012134	Mean age at follow-up was 32 months. Bayley exams were done at 18 months. Neurologic abnormalities and CP did not differ significantly across the gestational ages of 24 to 26 weeks. Between 67% and 89% were normal in each gestational age group. Significant differences (P = 0.036) related to gestational age were found in 18 month Bayley exam scores when group as normal borderline or deficient Normal / Deficient 24 wk 28% / 39% 25 wk 47% / 30% 26 wk 71% / 11% Significant differences (P = 0.008) related to gestational age were found in the combined end point of CP or an abnormal Bayley exam score: Neither / One / Both 24 wk 28% / 39% / 33% 25 wk 47% / 23% / 30% 26 wk 63% / 34% / 3%	All inborn infants	No data on funding source

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Author, Year	Associations found	Potential Biases	Comments
Singer 1997 98049057 Singer 2001 21163669	Evaluation at 36 months corrected age. VLBW, VLBW with BPD, full term (FT). Bayley MDI: VLBW 90 ± 16 (38-126); VLBW w/ BPD 84 ± 24 (10-116); FT 96 ± 12 (57-127) % with MDI below 70: VLBW 11%; VLBW w/ BPD 21% P = 0.001 for VLBW vs. VLBW w/ BPD Bayley PDI: VLBW 98 ± 20 (33-122); VLBW w/ BPD 84 ± 29 (8-127); FT 103 ± 15 (58-128) % with PDI below 70: VLBW 9%; VLBW w/ BPD 9%; FT 1% P = 0.001 for VLBW vs. VLBW w/ BPD At 3 years BPD predicted poorer motor outcome but not poorer mental outcome. **Receptive DQ**: BPD < VLBW < Term, p < 05 **Receptive DQ < 85:** BPD 49%, VLBW 34%, Term 30%, BPD < VLBW + Term p < .05 **Expressive DQ:** BPD < VLBW + Term, p < .05 **Expressive DQ<85:** BPD 44%, VLBW 25%, Term 25% BPD < VLBW + Term p < .05 **Communication DQ**: BPD < VLBW + Term, p < .05 **Communication DQ < 85:** BPD 43%, VLBW 31%, Term 28%, NS Rank order listing of risk factors in order of magnitude of effect and the number of communication DQ lowered by the risk factor: PDA lowered DQ by 13 points, Minority race by 6 points, lower socioeconomic status by 5 points, and higher neurologic risk by 5 points. p .001 **Bayley Scales MDI:** BPD 83.7 ± 24, VLBW 90 ±16, Term 96.4 ± 12, BPD < VLBW < Term, p< 0.05 **Bayley Scales PDI:** BPD 84.1 28, VLBW 97.4 19, Term 102.8 14 BPD < VLBW + Term, p< .05 **ROP:** BPD 43%, VLBW 4%, p= .001 **Seizures**: BPD 7%, **Neurologic score**: BPD 1.3 ± 2, VLBW 58 ± 1, p < .001	Single region, but at least it is a region Unclear if examiners were blinded to group status	Study was government funded

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Author, Year	Associations found	Potential Biases	Comments
Victorian Infant Collaborative study Group, 1997 98026322 ***This study is also in CNS table**	Birth weight < 1000g; assessed at 2 years corrected age. Cohort n DQ < -3 SD DQ –3 to –2 SD DQ –2 to –1 SD DQ> -1 SD '91-'92 237 5.9% 6.3% 13.9% 73.4% '85-'87 211 6.2% 4.3% 14.2% 75.4% Cohort n Mild CP Mod. CP Severe CP Any CP Blindness Deaf '91-'92 237 3.8% 1.7% 3.8% 9.3% 2.1% 0.8% '85-'87 211 NS NS NS 6.6% 4.3% 0.5% Cohort No disability Mild Disability Moderate disability Severe disability '91-92 n = 237 71.3% 14.8% 7.2% 6.8% '85-'87 n = 211 71.6% 15.6% 6.2% 6.6%	Incomplete reporting of demographic data, methods and results.	Study was government funded
Victorian Infant Collaborative study Group, 1997 97466059 Arch Dis Child	All children born outside the level III perinatal centers. Assessment at 2 years corrected age. 1985-1987 1991-1992 n 19 16 Cerebral Palsy 19.1% 12.5% Cognitive delay 19.1% 18.8% Blind 5.6% 6.2% Deaf 0 0 Sensorineural disability Mild 15.8% 6.2% Moderate 0 0 Severe 5.3% 12.5%	Incomplete reporting of demographic data, methods and results.	Study was government funded

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Author, Year	Associations found	Potential Biases	Comments
Cheung 1998 99059896	Mean MDI 81 ± 21, PDI 64 ± 22 Normal development 31% Neurodevelopmental delay 20% Disabled 50% Severe mental retardation 10% Spastic diplegic CP 30% Hemiplegic CP 10% <3rd %ile for weight 20% <3rd%ile for height 40% <3rd%ile HC 30% BPD 80% Need bronchodilators for CLD 10% Recurrent wheezing but did not need meds 40% Grade 4 IVH 20% Grade 3 IVH 20% VP shunt 30% PVL 10% Sensorineural hearing loss 10%	Very small sample size Descriptive study with no control group for comparison	No data on funding source
Finnström 1998 99041345	**CP** in 23-24 wks: 14%, in 25-26 wks 10%, =27 wks 3%, p<0.02 CP 25-26 wks AGA: 8%, SGA 24% **Major handicap by GA:** 23-24 wks: 14% 25-26 wks: 9% =27 wks: 3% **Major handicap by predictors:** Grade = 3 IVH and/or PVL: 29%, OR 5.6 (95%CI 2.4-12.9) Stage = 3 ROP 19%, OR 2.8 (1.1-7.6) Oxygen-dependent at 36 wks: 11%, OR 2 (0.9-4.1) PDA requiring treatment: 10%, OR 1.2 (0.5-2.8) Apgar score 0-3 at 1 min: 15%, OR 1.7 (0.7-4.0) Mechanical ventilation: 7%, OR 1.3 (0.4-4.5) After adjusting for GA, significant increased risk of handicap in infants with Grade = 3 IVH/PVL and Stage = 3 ROP **The mean height, weight and head circumferences were** significantly lower than reference values.	Exams done by infants' own pediatrician who is not blinded. Also they were not specifically trained in the evaluation so that results may be inconsistent. No control group. Scheffzek's categories not well defined. Infants were in the era of limited use of antenatal steroids and surfactant so that they may have been much sicker. How GA was determined not reported.	No data on funding source Possible that because of national recommendation that mothers should not be treated actively on fetal indications before completion of 25 weeks that only the fittest survive and this may underestimate Incidence of CP in this study. {Died by the follow-up exam (1) Left the country (6) Incomplete identification Number (1)}

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Author, Year	Associations found	Potential Biases	Comments
Gregoire 1998 98232532	Neurodevelopmental Outcome at 18 Months Control / BPD-1 / BPD-2 N: 76 / 48 / 93 Developmental quotient (DQ): 97.4 (15.6) / 97.9 (11.6) / 90.7 *(19.3) DQ when no grade 4 IVH or PVL: 97.4 (15.6) / 99.9 (9.1) / 93.0 *(19.3) Percent w/ DQ ≤ 93: 25% / 29% / 46%* Percent w/ DQ ≤ 82: 13% / 13% / 24% Total CP: 14% / 17% / 17% Severe CP: 13% / 13% / 17% Total disabilities: 29% / 31% / 50%** BPD-1: supplemental O2 at 28 days but not at 36 weeks PCA. BPD-2: supplemental O2 at 36 weeks PCA. *P < 0.05 for comparison between BPD-1 vs. BPD-2. ** P < 0.05 for control group vs. BPD-2 and for BPD-1 vs. BPD-2.	Exam of SGA infants in BPD-2 group Higher receipts of postnatal steroids in BPD-2 groups Higher rate of severe IVH in BPD-2 groups	Study was private and hospital funded
Kurkinen-Raty 1998 98387235 (All+Lung) ***sample from the same big population as 20284814**	Retrospective controlled cohort study of early PROM between 17 and 30 weeks of gestation. Assessments at one year corrected age. N = 55 for early PROM and 56 for control. Outcome / Early PROM / Control / OR (CI) Cerebral palsy: 18% / 16% / 1.2 (0.4, 3.1) Delayed motor Development: 9% / 16% / 0.5 (0.2, 1.7) Visual disability: 4% / 4% / 1.0 (0.1, 7.5) Hearing loss: 7% / 9% / 0.8 (0.2, 3.2) Good nuerosensory development: 67% / 61% / 1.2 (0.6, 2.2) Early PROM seems to be a major obstetric and neonatal problem with pulmonary ramifications extending beyond the neonatal period. However, most of these infants can be saved.	(None)	No data on funding source

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Author, Year	Associations found			Potential Biases	Comments
Lee 1998 98442293	**Growth, CNS and Audiology, and ophthalmology outcomes** for prematures<1250 g with candidemia/candida meningitis	Cases	Controls	1) Cannot exclude missed association due to the small number of patients analyzed n both groups	
	Growth:				
	1) No difference in Growth retardation:	7/14 survivors(50%)	11/21 survivors (50%)		
	CNS:	83 ±20	90 ±20 (p>0.05)		
	1) No difference in MDIs of survivors	71 ±21	87±18 (p<0.05)		
	2) Lower PDIs in survivors				
	3) No difference in overall Neurodevelopmental disabilities (NDDs)	4/14 (29%)	3/21 (14%) (p>0.05)		
	4) Cerebral palsy	4/14 (29%)	3/21 (14%)		
	Ophthalmology:				
	1) Vision loss	2/14 (14%)	1/21 (5%)		
	Audiology:				
	1) Hearing loss	2/14 (14%)	1/21 (5%)		
	(All the children with NDDs had Cerebral palsy with or without visual or hearing deficit)				
	Prematures<1250 g with candidemia/candida meningitis had: Higher Combined mortality and NDDs	60% (OR=3.9; 1.2-12.6)	28% (p< 0.05)		

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Author, Year	Associations found	Potential Biases	Comments
Lefebvre 1998 98387703	Assessed at 18 months corrected age. Divided into low, moderate and high-risk group based on Neurobiologic risk score (NBRS). Tested with Griffith's Developmental Scales. Griffith's Developmental Score Category Risk Group n Severe impairment, <80 All < 80 Low 50 0% 12% Moderate 37 22% 24% High 34 50% 71% Significance: for severe or any delay the NBRS was predictive, P < 0.0001 Risk Group n Severe CP (+) Any CP Low 50 0% 4% Moderate 37 13% 19% High 34 26% 41% Significance: NBRS predictive of CP, severe CP, P < 0.0009, any CP P < 0.0001	(None)	Study was privately funded
Millet 1998 98212544	*Motor deficits:* Diffuse brain damage (N=26); 14 *Moderate CP:* Diffuse brain damage (N=26); 6 *Visual impairment:* Diffuse brain damage (N=26); 12 *Sensorineural hearing loss*: Diffuse brain damage (N=26); 2 *Cognitive impairment*: Diffuse brain damage (N=26); 16 *Epilepsy(in..? spasm)* : Diffuse brain damage (N=26); 2	This paper has serious flaws There is little demographic information and sparse reporting of CNS outcome. No statistical testing is report	No data on funding source

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year	Associations found	Potential Biases	Comments
Piecuch 1998 98446413	**Neural/Neurosensory outcome** 1) Neurologic and cognitive outcomes were relatively stable over the 3 time periods (1989-1991, 1984-1986, 1979-1981) for infants of 1000-1499 g BW. 2) > 90% of the infants born in each time period were neurologically normal. 3) There was a non-statistically significant trend towards an increased number of infants with neurologic abnormalities in the more recent period. 4) The incidence of CP was stable over the 3 time periods. Born in a recent period vs Born in a midpoint period vs Born in an Early period • Normal: 168/186 (90%) vs 143/155 (92%) vs 102/109 (94%) • Suspect: 10/186 (5%) vs 3/155 (2%) vs 1/109 (1%) • Abnormal: 8/186 (4%) vs 9/155 (6%) vs 6/109 (5%) More than 80% of infants in each group had normal cognitive outcome. Cognitive outcome: • Average/Above average: 152/182 (83%) vs 122/150 (81%) vs 86/102 (84%) • 1-2 SD< mean: 23/182 (13%) vs 19/150 (13%) vs 12/102 (12%) • > 2 SDs< mean: 7/182 (4%) vs 9/150 (6%) vs 4/102 (4%) 5) MDI scores declined slightly over time. But, mean PDI scores and MDI scores were not "clinically" significant across the 3 periods. More recent periods the infants born were smaller, younger, and had longer CLD Mean PDI: 96.6 vs 98.5 vs 96.9; Mean MDI: 101.0 vs 103.4 vs 106.9 In all the infants from the 3 time periods: General Predictors evaluation: Univariate analyses of predictors showed different relationships between outcome depending on inborn or outborn, with inborn having better neurologic and cognitive outcome. Predictors associated with with poor neurologic/neurosensory (suspect and abnormal) or poor cognitive outcome (p< 0.02) were: Place of birth (outborns vs inborns); GA; male gender; ICH; CLD. When infants of suspect or abnormal neurologic outcome and infants of abnormal neurosensory outcome were grouped together and compared with infants of normal neurologic/neurosensory outcome (multivariate): For inborns: ICH, GA were predictors of poor outcome; For outborns:ICH, CLD were predictors of poor outcome. When infants of mild and moderate to severe cognitive deficits were grouped together and compared with infants of normal cognitive outcome (multivariate): For inborns: males had poorer outcome; For outborns: CLD was associated with poorer outcome	Concern about generalizability of findings in other populations with higher socieconomic status and higher maternal education. (For 50% of infants families were on public assistance and had maternal education of <12 yrs) Predictors were assessed for their association with the outcomes; but the outcomes were measured with different scales for the different age groups (Bayley, Stanford-Binet, McCarthy, Wechler Intelligence scale) and the mean age at assessment were different in the 3 periods	Severe cognitive delay may be apparent at 26 mo CA (the mean age of assessment of the youngest group in the study). However, subtle or late appearing cognitive problems may not have yet been diagnosed. Thus, the study had a limitation in detecting borderline cognitive or academic problems.

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part III

Author, Year	Associations found	Potential Biases	Comments
Sajaniemi 1998 99041674	The neurological outcome of preterm infants was: For Cerebral palsy: Free from major disabilities MDI 1) All prematures: 17.5% 82.5% 103 2) Prematures < 1000 gs: 23.5% 23.5% 98 3) Prematures > 1000 gs: 13.5% 85.6% 107 The developmental outcome: Preterm infants had significantly lower MDI scores when compared to full terms (Full terms 124) When temperament was considered: the premature children were significantly less active; more adaptive; less intensive; more positive in mood and had lower sensory threshold than the healthy control term children. When behavior was assessed (Infant's Behavior Records): the preterms were significantly less goal directed; less attentive and; had lower in endurance than the controls. When Bayley neurodevelomental was assessed: 1) The preterms performed significantly less well than the controls. 2) Low Bayley scores correlated with temperament scores of high rythmicity, positive mood, low persistence and high threshold 3) Low Bayley scores correlated with IBR scores 4) No strong relationship between temperament characteristics and cognitive performance. Preterm infants had significantly lower MDI compared to full terms: • Preterm infants were different in 5/9 items of temperament profile compared to full terms: less active ($p<0.008$), more adaptive ($p<0.02$), less intense ($p<0.01$), more positive in mood ($p<0.0004$), lower in threshold to respond ($p<0.0003$) • Preterm infants were different in 3/5 items in IBR profile, when compared to full terms: less goal directed, less attentive, lower in endurance Predictors evaluation: • From the perinatal risk factors: pre-eclampsia, SGA, PVL and IVH were not associated with developmental outcome or temperament profiles. • PVL, IVH were associated with shorter attention span (1/5 items in IBR profile); when preterms compared to full terms. • Duration of NICU stay was not associated with Bayley score • Duration of ventilation was not associated with Bayley score • Duration of ventilation and days in NICU were associated with the 5 items of IBR profile; Duration of ventilation was associated with 1/9 items of temperament profile	• Post hoc multiple comparisons were done between preterms and full terms for the multiple individual items of the tests used. • Cannot exclude selection bias • No matching between groups cannot exclude the presence of confounders. • Interactions between predictors may have masked some real associations; possible interactions were not formally tested • Cannot exclude diagnosis bias, as no information is given on the blinding of the personnel doing the outcome evaluation of the child's PMHx.	

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part III

Author, Year	Associations found	Potential Biases	Comments
Scherjon 1998 98429216	Predictors **for Neurodevelopmental outcomes** (Univariate analysis) Adverse neurodevelopmental outcome at 3 years, measured with the Hempel test, was related to: 1) neonatal cranial ultrasound abnormalities of neonatal periventricular echodensities- as a sign of cerebral ischemia or intracranial haemorrhages ($p< 0.0001$) 2) low head circumference at 3 years. (when compared to normal and moderate abnormal findings) ($p< 0.0001$) Hempel test was not related to the umbilical/cerebral artery pulsatility index (raised vs normal) ($p=0.23$) Fetal growth retardation (IUGR) or gestational age was not related to behavioral aspects, language and speech skills using a parental questionnaire. Abnormal neurosonographic findings had an influence on Hempel outcome, only if these findings occurred in combination with a normal U/C ratio. However, abnormal neurosonographic findings with raised U/C ratio were not associated with a poor Hempel outcome. (Raised U/C ratio reflects a more favorable adaptation to prematurity related risks, preventing the infant from having severe intracranial pathology) Predictors for **Growth outcomes** at 3 yrs (Univariate model) In preterm infants born 26-33 wks, lower median HC at 3 yrs was associated with 1) fetal Doppler findings of raised Umbilical/cerebral artery pulsatility index (U./C ratio) (vs Normal U/C ratio) ($p=0.01$) Weight or height at 3 yrs was not associated with this predictor. Predictors for **Growth and Neurodevelopmental** outcome (multivariate) 1) Cranial U/S findings of IVH and ED were associated a) with Hempel outcome ($p<0.001$), and b) with HC at 3 yrs. ($p=0.01$) (it is not clear if it refers to moderate or abnormal U/S classification, or both) 2) U/C ratio, fetal growth ratio and GA were not associated with Hempel outcome	Cannot exclude possible confounders between compared groups.	The methods used for evaluation of qualitative behavioral and language differences at the age of 3 years between infants with and without placental insufficiency, possibly was not sensitive enough. There was blinding for the Hempel outcome assessment on the patients PMH or cranial U/S findings. The focus of this study was on motor development and quality of motor function. However, as there is weak association between neurodevelopmental outcome at 3 yrs and at school age yrs, it remains to reevaluate these children for their cognitive function at school age.

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Author, Year	Associations found	Potential Biases	Comments
Cheung 1999 99146391	*Mental score:* Days of ventilation: (N=64) <0.0001 *Motor Score:* Days of ventilation: (N=164) <0.004 *Mental Score:* Grade of IVH: (N=164) 0.003 *Motor Score:* Grade of IVH: (N=164) <0.0001 *Mental Score*: Infants <1250g with gr. 3 or 4 IVH: (N=50) <0.001 *Motor Score*: *Infants <1250g with gr. 3 or 4 IVH: (N=50) <0.001*	(None)	No data on funding source

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part III

Author, Year	Associations found	Potential Biases	Comments
Duvanel 1999 99207097	There was no association of hypoglycemia with scores in Griffith's test at 6, 12, 18 months and in the McCarthy's test at 5 years. There was association of hypoglycemia with significantly lower scores in 2 items of the McCarthy's test (the perceptive index and the motricity index score) at 3.5 years Repeated episodes of hypoglycemia were associated with significantly decreased scores for 2/ 6 items in the McCarthy's test (perceptive performance and motricity scale index) only at 3.5 years. (p< 0.05) Hypoglycemic Euglycemic group One episode of hypoglycemia: Mean MDI perception score at 3.5 yrs: 44.00 50.33 (p<0.01) >6 episodes of hypoglycemia MDI perception score at 3.5 yrs 44.89 50.33 (p<0.05) >7 episodes of hypoglycemia: • MDI perception score at 3.5 yrs (P<0.01) 42.64 50.33 • Motricity index score at 3.5 yrs (p<0.05) 43.00 52.53 Moderate hypoglycemia (11-29 mg/dl) was associated with significantly lower score in 2/6 items (perceptive performance and motricity scale index) in the McCarthy's test only at 3.5 years. (p< 0.005) No data on the association between the severity of hypoglycemia and the outcomes at 6, 12, 18 months and 5 years. (No complete data reporting) Infants with recurrent mild hypoglycemia had lower neurodevelopmental scores than the group with 1 unique severe episode of hypoglycemia. (Multiple subgroup comparisons, between subgroups of the independent variable and subgroups of the dependent variable) Hypoglycemia was not associated with growth rates for Weight, length, and HC at intervals 6-18 months, 6 mo-3.5 yrs, or 6mo -5 yrs. Hypoglycemia was associated with significantly reduced HC at 12, 18 mo and 5 yrs. (p<0.05)	1) Selection bias 2) Information bias (in the measurement of the independent variable/glucose levels) 3) Confounders between the 2 groups 4) Multiple subgroup comparisons. Hypothesis generating analyses.	Selected Population/Potential Selection bias: Apparently a high-risk population was studied as the frequency of hypoglycemia identified was much higher than usually anticipated. Methods: Not clear for which parameters the matching between the 2 groups was done. Did not describe the flow of patients (Enrolled, excluded, lost to follow up, eligible for the analysis) Statistical analysis: No predefined in the Method section of primary and secondary outcomes to be studied. Many exploratory, hypothesis generating, subgroup analyses, which were not predefined in the Method sections. Information bias: Not consistent measurement of the predictor (glucose level) across different categories of hypoglycemia. Dextrosticks if glucose> 36mg/dl vs glucose analyzer if glucose<36 mg/dl)

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year	Associations found	Potential Biases	Comments
Pennefather, 1999 20002011 Pennefather, 2000 20217908 *** This study is also in eye table**	Strabismus in 70/558 (12.5%) infants GA<32 week . **The incidence of strabismus increased with decreasing** GA (p=0.0004), increasing severity of ROP (p=0.0001), and decreasing general developmental quotient (GMDS) (p<0.0001). Stabismus present in 28 (52%) of patients with CP (P< 0.001) **OR (95% CI) of Strabismus if following predictor was present:** Cicatricial ROP: 4.94 (1.1-22.12), p0.037 Fam Hx of Strabismus: 4.15 (2.19-7.88), p<0.00005 Refractive Error: 2.71 (1.3-5.66), p=0.008 GMDS 78-100: 3.34 (1.46-7.64), p =0.004 GMDS <77: 46.2 (17.1-125), p<0.00005 This study confirms findings of other studies that strabismus is increased in premature infants with decreasing GA and is increased with increasing severity of ROP and CP. Independent factors related to strabismus are cicatricial ROP, refractive error, family hx of strabismus, and developmental delay (especially delayed hand-eye coordination)	Prospective evaluation but retrospective collection of neonatal data; therefore, probable incomplete collection of variable reason for present and absent data No demographic data was report (the cohort was described elsewhere)	No data on funding source

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year	Associations found	Potential Biases	Comments
Ambalavanan 2000 21031370	ELBW: MDI<68 : 12% PDI<68: 20% Major handicap: 28% CP:28% MR 16% Post-hemorrhagic hydrocephalus: 5% Deaf 1.4% Blindness 1% Predictors of major handicap (Low MDI and/or PDI): Grade of IVH, PVL, absence of chorio (in this population, not in most others), NEC≥II; race; multiple gestation, BPD, maternal education For ELBW infants without IVH, the prevalence of major handicap, low MDI, and Low PDI was 25%, 17%, 16%, respectively. For ELBW infants with grade III IVH, the prevalence of major handicap, low MDI, and Low PDI was 33%, 29%, 24% respectively. For ELBW infants with grade IV IVH, the prevalence of major handicap, low MDI, and Low PDI was 69%, 44%, 63% respectively. This study identifies major determinants of adverse neurodevelopmental outcome (i.e. major handicaps, low MDI, low PDI) of ELBW (<1 kg) infants born 1990-1994. Grade of IVH is strong predictor of adverse outcome. But note large % of ELBW without IVH who had major handicap, low MDI, and Low PDI. **BPD** was a significant determinant of low MDI and PDI. Mat education level was significant determinant of neurodevelopmental outcome. NEC, race, multiple gestation, PVL independently contributed to poor outcome in ELBW infant. Lower BW predicted low PDI.	Retrospective, relatively small samples size (218).	No data on funding source

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part III

Author, Year	Associations found	Potential Biases	Comments
Cioni 2000 20150341	Multivariate analysis found that periventricular leukomalacia in premature infants is highly, significantly correlated with visual impairment and abnormal neurodevelopment at 1 and 3 years age. The degree of visual impairment correlated well with degree of neurodevelopmental abnormality at 1 and 3 years age. Strong association between visual impairment and involvement of optic radiation on MRI. 28 of 29 infants had abnormal neurological examination at follow-up (6 mild abnormal; 22 had CP). 23/29 premature infants with PVL abnormality on MRI had at least one abnormality of visual function, and 50% had multiple visual function abnormalities. 8/29 severe 'fixation and following' disorders 19/29 had strabismus abnormal grating visual acuity 13/29 reduced visual field 9/29 OKN abnormalities 17/29	(None)	Study was government funded Visual function plays a strong role in early global development. But the presence of exceptions to these results also illustrate the complex, multifactorial nature of neurodevelopmental outcome. This study also illustrates the importance of a comprehensive assessment that includes various aspects of visual function. No single visual assessment will detect all visual abnormalities.

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Author, Year	Associations found	Potential Biases	Comments
Hack 2000 20358826	MDI Score < 70: CLD: 55% (49/89); 2.18 (1.20-3.94) MDI Score<70 (multi stepwise logistic regression) Male sex: 2.73 (1.52-4.92) Social risk: 1.48 (1.09-2.00) CLD: 2.18 (1.20-3.94) OR adjusted for sex, social risk & BW: Gr III-IV IVH: 50% (16/32); 8.55 (3.52-20.76) 50% (8/16); 4.45 (1.54-12.84) 50% (17/34); 5.48 (2.41-12.47) CLD: 30% (27/89); 3.09 (1.51-6.35) Sepsis: 14% (13/93); 3.47 (1.16-10.36) Jaundice: 26% (6/23); 5.15 (1.63-16.22) Mult. Stepwise Logistic regression: Male sex: 2.79 (1.02-7.62) Sepsis: 3.15 (1.05-9.48) Jaundice: 4.80 (1.46-15.73) Predictors of neurologic abnormality were a severely abnormal finding on cerebral ultrasound (OR, 8,09; 95% CI 3.69-17.71) and chronic lung disease (OR 2.46; 95% CI 1.12-5.40); predictors of deafness were male sex (OR 2.79 95% CI 1.02-7.62), sepsis (OR 3.15 95 % CI 1.05-9.48), and jaundice (maximal bilirubin level >171)		The authors concluded that there is an urgent need for research into the etiology and prevention of neonatal morbidity.

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Author, Year	Associations found	Potential Biases	Comments
Jankov 2000 20188680	Infants CPR in delivery room -9 survived to discharge 8/9 were free of severe neurologic disability 1/9 was legally blind DR resuscitation beyond PPVin <750 gms was associated with high mortalilty but without unnecessary prolongation of life Persistent Apgar score <5 and delayed onset of respirations beyond 5 mins in CPR recipients were associated with death or severe disability. Did not find a high rate of severe neurodevelopmental disability in CPR recipients	Incomplete disclosure of data as it relates to the subgroups Small sample size Opposite results to other studies might be explained by decisions in many cases not to resuscitate infants that are extremely high risk which would be resuscitated in other centers	No data on funding source

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Author, Year	Associations found	Potential Biases	Comments
Kurkinen-Raty, 2000 20284814 ***sample from the same big population as 98197235**	**CLD at 1 year age:** Indicated PT delivery: (81) 12/81 (15%) Spontaneous PT delivery: (94) 3/94 (3%) RR 4.6 (1.4, 1.6) **Growth:** Indicated PT delivery: (81) Spontaneous PT delivery: (94) Weight RR =0.03 (-5.3, 0.3) L RR = 0.002 HC RR = 0.03 **CP:** Indicated PT delivery: (81) 5/81 (6%) Spontaneous PT delivery: (94) 10/94 (11%) RR=0.6 (0.25-1.6) **Delayed motor:** Indicated PT delivery: (81) 8/81 (6%) Spontaneous PT delivery: (94) 8/94 (9%) RR 1.2 (0.5-3.0) **Visual disability:** Indicated PT delivery: (81) Spontaneous PT delivery: (94) RR =1.9 (0.5, 7.8) **Hearing loss:** Indicated PT delivery: (81) Spontaneous PT delivery: (94) RR =1.9 (0.5, 7.8) 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 yr age. More infants in 'indicated' group were SGA and were significantly smaller than control group at 1 yr in Wt, HT, and HC. There was no difference between groups in neurosensory outcomes.	Outcome not well defined Difficult to know if lack of difference between groups is due to sample size or event rate.	No data on funding source

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Author, Year	Associations found	Potential Biases	Comments
Marlow 2000 20150342	Pulmonary and Other predictors evaluation for **Audiology outcome**. Children with sensorineural hearing loss [15] as compared to control group[30] had longer periods of: 1) Intubation, (14 ds vs 2 ds) 2) Ventilation (34 ds vs 6 ds) 3) Oxygen therapy (57 ds vs 10 ds) 4) Acidosis (12 ds vs 0.5 ds), and 5) More treatments with dopamine (33% vs 7%)or 6) Furosemide (87% vs 53%) 7) Neither P/T of aminoglycosides 8) nor duration of jaundice 9) or level of bilirubin varied between the 2 groups. SNHL was more likely when : 1) netilmicin use coexisted with the peak of bilirubin (87% vs 14%)_ 2) when acidosis occurred when bilirubin was over 200 ?mol/l, (31% vs 4%) 3) when furosemide was used in the face of high creatinine levels (64% vs 27%) 4) when furosemide was used with netilmicin (67% vs 37%) **CNS outcome at 12 mo:** At 12 months of age evidence of cerebral palsy was present in 7/15 (47%) of children with SNHL vs 2/30 (7%) of children without SNHL.(p=0.022)	1) Very small sample size (cases with SNHL only 15) 2) Analyzed too many predictors and combination thereof, for very few outcomes. Very wide confidence intervals; and even those predictors found to be associated with the SNHL this may have been due to chance. 3) The association found between SNHL and cerebral palsy was not based on an adjusted analyses for possible confounders; 4) The 2 groups were different in many factors that were associated with both SNHL and CP	Not reported source of funding

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Author, Year	Associations found				Potential Biases	Comments
Victorian Infant Collaborative study Group, 2000 20307288 ***some subjects were overlapped with Doyle, 2001**		Cortocosteroids	No Cortocosteroids	P-value	(None)	No data on funding source
	n	98	195	Cerebral		
	Palsy	22.7%	3.6%	<0.0001		
	Blindness	5.2%	0.5%	<0.02		
	Deafness	1%	1.5%	ns.		
	IQ scores			<0.0001		
	=-1SD	46.4%	68.2%			
	-2 SD to <-1 SD	27.8%	24.1%			
	-3 SD to <-2 SD	13.4%	4.6%			
	< -3 SD	12.4	3.1			
	Sensorineural disability			<0.0001		
	Mild	26.8%	23.6%			
	Moderate	18.6%	6.7%			
	Severe	13.4%	3.6%			
	Subgroup case-control study: cases (subjects with cortocosteroids treatment) and controls (subjects w/o with cortocosteroids treatment) were well matched in most perinatal variable					
		Cortocosteroids	No Cortocosteroids	P-value		
	n	60	60	Cerebral		
	Palsy	21.7%	5.0%	<0.002		
	Blindness	1.7%	1.7%	ns.		
	Deafness	1.7%	3.3%	ns.		
	IQ scores, SDS	-1.26	-0.86	<0.05		
	Sensorineural disability					
	Mild	26.7%	26.7%			
	Moderate	21.7%	6.7%			
	Severe	10%	8.3%			

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Author, Year	Associations found	Potential Biases	Comments
Wood 2000 20373840	Infants 22-25 weeks GA developmentally assessed at median 30 months • 138/283 had disability 49% (64 met criteria for severe disability) • 49% no disability • 53/283 severely delayed 19% (Bayley below 3 SD) • 32/283 2-3 below SD 11% • 28 severe neuromotor disability 10% • 7 blind or perceived light only 2% • 8 hearing loss that was uncorrectable or required hearing aids 3% Survived without overall disability 22 wks----------0.7 % 23 wks----------5% 24 wks----------12% 25 wks----------23% Severe disability at 30 months 22 ----------0.7% 23 ----------3% 24----------6% 25----------9% • no relation between morbidity pattern and either gestational age &multiple birth • boys were likely to be disabled than girls	(None)	Severe disability common children born extremely prema ture

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
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Author, Year	Associations found	Potential Biases	Comments
Doyle 2001 21326609 Victorian Infant Collaborative study Group, 1997 97290716 J Paediatr Child Health ***some subjects were overlapped with 20307288 (stated in text)** ***possibly overlapped with 98026322**	Evaluation at 5 years corrected age: **CP :** 23-27 wk survivors (11.3%) 25/221 FT controls (0%) Blindness : 23-27 wk (1.8%) 4/221 FT control 0% **Deafness : 23-27 wk (0.9%) 2/221** FT control 0% **IQ <-2 SD: 23-27 wk (15.4%) 34/221** **Major neurosensory disability** 23 –27 wk (19.6%) 44/225 FT control (4.1%) 10/245 **Major disability among survivors** 23 wk GA: 2/5 (40%) 24 wk GA: 7/21 (33%) 25 wk GA: 13/51 (25%) 26 wk GA: 17/71 (24%) 27 wk GA: 5/79 (6%) Overall 23-27 wk: 19% **OR for survival with major disability at 5 years:** OR each 1 wk increase in GA = 0.59 (95% CI 0.43, 0.8) **Prognostic factors with major disability at 5 years:** IVH, cystic PVL, surgery during primary hospitalization, postnatal steroid treatment. **Rates of survival free of major disability for surviving PT infants:** None 96/103 =93% One 59/71 =83 % Two 23/43 =53 % Three 3/9 =33% Four 0/1 = 0 Evaluation at 2 years corrected age. Data shown are for births in 1991-1992. Gestational age / Sensorineural disability (% of survivors) n / Severe / Moderate / Mild / None 23 weeks 5 29% 20% 40% 20% 24 weeks 21 14.3% 19% 33.3% 33.3% 25 weeks 51 5.9% 21.6% 25% 47% 26 weeks 68 8.8% 11.8% 20.6% 58.8% 27 weeks 74 1.4% 10.8% 23% 64.9% Overall 219 6.4% 14.6% 24.2% 54.8% Decrease in disability with increase in gestational age was significant, p = 0.014. Also showed significant fall in severe disability with increase in gestational age, Odds ratio = 0.58 (0.36-0.94) Comparison of cohorts born in 1985-1987 vs. 1991: 1992 did not demonstrate any difference between cohorts.	Perinatal data lacking on some infants, Especially outborn (in level II or I) Different methods of testing IQ Different times of assessing Neurodevelopmental outcome Some children not evaluated at 5 years (evaluated at 2 years) 210/401 preterm infants were assessed at both 2 and 5 years The classification of disability or no disability was the same at both 2 and 5 years (90.5% agreement; k=0.691) Inadequate discussion of study population, Demographic Also various surrogate data	Study was government funded

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Author, Year	Associations found	Potential Biases	Comments
Gaillard 2001 21221175	Predictors for **Neurodevelopmental outcome:** 1) Shorter length of ventilation (beyond 27(but not 50) postnatal days) was associated with better neurodevelopmental outcome : 59% (33/56) neurodevelopmentally normal or only mildly disabled survivors vs 25% (7/28) with more prolonged ventilation(> 49 ds) *Ventilated beyond 27 (but not 50)ds vs Ventilated beyond 49 ds* Total: 56 vs 28 Survived: 48/56 (86%) vs 14/28 (50% Normal neurodevelopmentally: 26/48 (54%) vs 5/14 (36%) Mild disability: 7/48 (15%) vs 2/14 (14%) Moderate disability: 11/48 (23%) vs 4/14 (29%) Severe disability: 4/48 (8%) 3/14 (21%) 2) Number of days "off"" ventilator was not associated with the neurodevelopmental outcome at 3 yrs neither in the groups of 27-49 postnatal ds ventilation nor in the group of >49ds ventilation (but had only 1,4 and 9 survivors in the 3 subgroups respectively) *Ventilated beyond 27 (but not 50)ds and O ds "off" ventilator vs 1-7 ds "off" ventilator vs > 7 ds off ventilator* Total: 18 vs 17 vs 21 Survived: 13 (72%) vs 15 (88%) vs 20 (95%) Neurodevelopmentally normal: 8 (44%) vs 7 (41%) vs 11 (52%) Mild disability: 2 (11%) vs 2 (12%) vs 3 (14%) Moderate disability: 3 (17%) vs 4 (24%) vs 4 (19%) Severe disability: 0 vs 2 (12%) vs 2 (10%) (In the second component: comparison of the retrospective cohort with the historical control) 3) Birth in a period where antenatal steroids and exogenous surfactant was more routinely used was associated with better neurodevelopmental outcome (69% vs 40% and 45% respectively in the 2 historical control cohorts)	In First component: Retrospective cases control design: 1) the 2 groups were unmatched for possible confounders, thus cannot exclude false associations 2) Cannot exclude selection Bias as only 62 survivors were analyzed from the 84 initially included in the 2 groups In the Second component: 3) Problems of confounders due to historical control group could be even greater	ND

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Author, Year	Associations found	Potential Biases	Comments
Roth 2001 21262686	Neurodevelopment Impairment: Liner array- all impairments 58 (28%) Disabling impairment 24 (12%) Mech sector all impairments 207 (36%) Disabling impairment 80 (14%)	Groups outcome into large categories of Disability unable to specify motor vs cognitive Vs hearing vs vision	

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Part III

Author, Year	Associations found	Potential Biases	Comments
Saigal 2001 21376729 *** Important paper**	Neurosensory Impairment:: ELBW 28%, FT Controls 2%, p= 0.001 Growth: Weight: diff. between ELBW and FT (mean z scores) –5.78 (p<0.0001) Visual Problems: ELBW 57%, FT Controls 21%, p=<0.001 (OR 5.1, CI 2.89-9.05) Current Health Problems (multiple/patient): ≥3 Health Problems: ELBW 35%, FT Controls 7%, p<0.0001 Past Health Problems: Seizures: ELBW 11%, FT Controls 2%, p<0.005 Asthma: ELBW 25%, FT Controls 14%, p=0.05 Recurrent bronchiolitis/pneumonia: ELBW 14%, FT Controls 3%, p=0.005 Current (at 12-16 yr age) Functional Limitation (Table 4 page 411) (multiple/patient) Visual difficulty: ELBW 57%, FT Controls 21%, p<0.001 Hearing Difficulty: ELBW 7%, FT Controls 5%, ns. Emotional problems: ELBW 4%, FT Controls 1%, ns Mental problems: ELBW 4%, FT Controls 1%, ns. Clumsiness: ELBW 25%, FT Controls 1%, p<0.001 Developmental Delay: ELBW 26%, FT Controls 1%, p<0.001 Learning Disability: ELBW 34%, FT Controls 10%, p<0.001 Hyperactivity: ELBW 9%, FT Controls 2%, p=0.04 Reduced self-abilities: ELBW 5%, FT Controls 0%, p=0.02 Limitation in school or in normal activity: ELBW 31%, FT Controls 9%, **p<0.002** Any functional limitation: **ELBW 81%, FT Controls 42%, p<0.001** Functional limitation/child [Mean (SD)]**: ELBW 2.0 (1.8), FT Controls 0.6 (0.8), p<0.001** Utilization of Health Care Resources: Pediatrician: **ELBW 34%, FT Controls 14%, p<0.0002** Ophthalmologist: **ELBW 62%, FT Controls 34%, p<0.0001** Ear/nose/throat: **ELBW 14%, FT Controls 6%, p<0.05** Occupational therapist: **ELBW 7%, FT Controls 1%, p=0.002** Speech therapist: **ELBW 8%, FT Controls 0%, p<0.002** Special Education: **ELBW 48%, FT Controls 10%, p<0.0001** Prescription Glasses: **ELBW 36%, FT Controls 10%, p<0.001**	Didn't specify exclusion criteria but these are implied based on clear industry criteria Limits to generalizability: 1) different era of natural care 2) white race 3) access to universal health care in Canada	Study was private funded

Evidence Table 1. Studies Evaluating Association of LBW and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part III

Author, Year	Associations found	Potential Biases	Comments
Schmidt 2001 21298249	1) There was no difference in primary outcomes between the 2 groups at 18 months of age. 2) Among the 574 infants who were assigned to prophylaxis with indomethacin, 271 (47%) died or survived with impairment as compared with 261 of 569 infants (46%) assigned to placebo (OR: 1.1; 95% Confidence intervals; 0.8-1.4) 3) In VLBW infants, prophylaxis with indomethacine does not improve the rate of survival without neurosensory impairments at 18 months of age 4) There was no difference in any of the secondary outcomes between the 2 groups , at 18 months of age. **Primary: Composite / CNS Outcomes:** **Indomethacin vs. Placebo** • Death or impairment 271/574(47%) vs. 261/569 (46%) • Death before 18 mo 121/595 (21%) vs 111/594 (19%) • Cerbral palsy 58/467 (12%) vs 55/477 (12%) • Cognitive delay (MDI<70 by Bayley scale 118 /444 (27%) vs 117/457 (26%) **Audiology outcome:** • Hearing loss requiring amplification 10/456 (2%) vs 10/466 (2%) **Ophthalmology outcome:** • Bilateral blindness 9/456 (2%) vs 7/472 (1%) (Odds ratios adjusted for BW stratum and Center) **Secondary CNS outcomes** were not affected by indomethacin administration: • Hydrocephalus requiring shunt 15/470 (3%) vs 9/480 (2%) • Seizure disorder 8/470 (2%) vs 7/483 (1%) • Microcephaly 49/461 (11%) vs 54/475 (11%) Kaplan Meier estimates of survival in the 2 groups: • 0 months n=601 vs 601 • 6 months n=479 (80%) vs 490 (82%) • 12 months n=473 (79%) vs 487 (81%) • 18 months n=470 (78%) vs 483 (80%)		1) By using the Bayley test at 18 mo the authors found that more than one quarter of all surviving infants had moderate to severe cognitive delays, defined by MDIs< 70. The validity of the MDI score at this age as a predictor of later intellectual functioning remains to be determined. 2) At a post hoc calculation the study had a 90% power to detect a 20% reduction in risk, had it existed 3) Authors report that the outcome assessments were done blindly by investigators unaware of treatment groups assignments. 4) Authors report that they had almost complete ascertainment for the primary outcome at 2 yrs of age.

Evidence Table 2. Randomized Controlled Trials for LBW Infants and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Casiro 1995 95264245	Location: Canada Years of Birth: 1988- 1990 Mean GA (range), wk: Experiment: 25.8±1.6 Control: 24.8±1.1 Mean BW (range), g: Experiment: 652±64 Control: : 661±52 Male: Experiment: 40% Control: 40% Race: White Experiment: 6% Control: 14% Enrolled: 113 (111 controls) Evaluated: 47 (42 controls) Number of sites: 13	BW 500-749 g Informed consent Mechanical ventilation required within 24 hr. b/o RDS A/A PO2 ratio< 0.22	"Exclusion criteria for this study were the same as those used in an earlier trial of synthetic surfactant" (Long W, Thompson T, et al., 1991) Died by age of 1 year	Experiment: Exosurf (47) Control: Placebo (42)	Randomized Controlled Trial

Evidence Table 2. Randomized Controlled Trials for LBW Infants and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Gerdes 1995 95264241	Location: US Years of Birth: 3/1989-4/1990 Mean GA (range), wk: Experiment 1: 27.2±1.7 Experiment 2: 27.2±1.8 Mean BW (range), g: Experiment 1: 907±121 Experiment 2: : 911±125 Male: Experiment 1: 55% Experiment 2: 56% Race: Experiment 1: White 55%, Black 37%, Hispanic 4%, Other 5% Experiment 2: White 60%, Black 30%, Hispanic 5%, Other 5% Enrolled: 826 Evaluated: 508 Number of sites: 33	Mothers who were expected to deliver premature infants with BW 700-1100 g	All exclusion prenatal. 1) Proven fetal lung maturity 2) Known malformation or chromosome anomaly 3) Fetal growth retardation 4) Hydrops 5) Purulent amnionitis 6) Maternal heroin addiction 7) Obstetric decision not to support fetus Postnatal exclusions: 1) Major malformation 2) ≥3 minor anomalies 3) Hydrops	Experiment 1: One doses surfactant (244) Experiment 2: Three doses surfactant (264)	Randomized comparison trial (1 year)

Evidence Table 2. Randomized Controlled Trials for LBW Infants and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
O'Shea 1998 98167528 98190123 ***also in CNS table** ***overlapped sample as 98049056**	Location: US Years of Birth: 1978-89; 1990-94 Mean GA (range), wk: Born in 1978-1989: Cases: 28(24-33) Unmatched controls: 29 (23-39) Matched controls: 28 (24-34) Born in 1990-1994: 28.0±2.9 Mean BW (range), g: Born in 1978-1989: Cases: 1021 (520-1500) Unmatched controls: 1150 (580-1490) Matched controls: 1095 (580-1490) Born in 1990-1994: 1039±291 Male: Born in 1978-1989: Cases: 54% Unmatched controls: 50% Matched controls: 51% Born in 1990-1994: 51% Race: Born in 1978-1989: Cases: 45% African-American Unmatched controls: 35% African-American Matched controls: 32% African-American Born in 1990-1994: 56% White Enrolled: 1978-1989 (1559); 1990-1994 (1264) Evaluated: 1978-1989 (80 cases, 240 controls); 1990-1994 (723) Number of sites: 2	BW 500-1500g, admitted to the 2 intensive care nurseries that served the 17 countries in NW N. Carolina. Birth at only tertiary OB center in region Survived to age 1 year corrected age Cases: diagnosis of any subtypes of cerebra palsy Controls: VLBW infants born closest in time to the respective case, who after examination at 1 year of age were felt to be free of any signs of cerebra palsy	Major congenital anomaly	Born in 1978-1989: Cases: CP (80) Unmatched controls (160) Matched controls (80) Born in 1990-1994: VLBW infants: 723	Case-control study (1 year corrected age)

Evidence Table 2. Randomized Controlled Trials for LBW Infants and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
O'Connor 2001 21376723	Location: US Years of Birth: 1996-1998 Mean GA (range), wk: 29 (27-31) Mean BW (range), g: 1253 (965-1543) Male: 39% Race: ND Enrolled: 376 Evaluated: 246 (126 controls) Number of sites: 8	GA < 33 weeks and BW 750-1805 g Completed the study to 12 months' CA	Serious congenital abnormalities, major surgery prior to enrollment/ randomization. PVL/IVH > grade II Maternal Incapacity Liquid ventilation Severe asphyxia Uncontrolled systemic infection at enrollment	Sample 1: EHM-T fed infants (43), reference group only, not included in analyses At 12 months: Sample 2: AA+OHA (fish/fungal) (120) Sample 3: AA+DHA (egg-TG/fish) (126) Control: formula-fed infants (126)	Randomized controlled trial (12 months)

Evidence Table 2. Randomized Controlled Trials for LBW Infants and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Casiro 1995 95264245	Cardiovascular/Pulmonary: Exosurf vs. placebo	ND	**CNS:** Motor delay Cerebral palsy Cognitive delay Severity impairment **Ophthalmology**: ROP **Growth**: Height, weight, head circumference **Other:** Re-hospitalization in 1st year of life	Bayley Scales of Infant Development: MDI and PDI The details of ophthalmologic examination, 1-year follow-up, health status evaluation were described in elsewhere (Courtney SE, Long W, et al., 1995)
Gerdes 1995 95264241	Cardiovascular or Pulmonary: Surfactant use	ND	**CNS:** Cerebral palsy Cognitive delay Mental retardation **Ophthalmology:** Visual impairment, Blindness **Audiology:** Hearing Disorder, Deafness **Pulmonary:** Asthma e/o CLD Respiratory support @ 1yr **Growth**: Height, Weight, HC **Other**: hospital re-admissions, h/o surgery	Mental retardation Bayley Scales MDI<69

Evidence Table 2. Randomized Controlled Trials for LBW Infants and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
O'Shea 1998 98167528 98190123 ***also in CNS table** ***overlapped sample as 98049056**	General predictors: Birth weight GA CNS predictors: IVH White matter disorder Periventricular leukomalacia Ventriculomegaly/Ventricular dilation Other: Infectious disease Perinatal factors	Hemorrhage disease diagnosed by Cranial US finding	**CNS:** CP	CP including spastic hemiplegia (involvement of an arm and leg on the same side of the body), spastic diplegia (involvement of the both legs with minimal to no involvement of the arms); and, spastic quadriplegia (involvement of all four extremities)
O'Connor 2001 21376723	Other: Nutrition/growth	ND	**CNS:** Motor delay Cognitive delay Other: information processing languages **Ophthalmology:** Visual Acuity **Growth:** Weight Length Head circumferences	 Bayley scales – PDI; MDI Teller visual acuity cards

Evidence Table 2. Randomized Controlled Trials for LBW Infants and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part III

Author, Year	Associations found	Potential Biases	Comments
Casiro 1995 95264245	Assessed at one year corrected age. No significant differences between placebo group and Exosurf group for: Bayley MDI (Placebo 79 ± 22 vs. Exosurf 87 ± 20) Bayley PDI (Placebo 73 ± 18 vs. Exosurf 81 ± 19) Percent of patients with Bayley MDI < 69 (22% vs. 21%) Percent of patients with Bayley PDI < 69 (29% vs. 19%) No significant differences between placebo and Exosurf groups for: No impairment (38% vs. 55%, Placebo vs. Exosurf) Any impairment (62% vs. 45%, Placebo vs. Exosurf) Serious impairment (41% vs. 32%, Placebo vs. Exosurf) No significant differences between placebo and Exosurf groups for: Bilateral sensorineural deafness: 7% vs. 9%, Placebo vs. Exosurf) Blindness: (7% vs. 2%, Placebo vs. Exosurf) No significant difference in height, weight or head circumference.	All patients had RDS requiring mechanical ventilation	No data on funding source

Evidence Table 2. Randomized Controlled Trials for LBW Infants and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part III

Author, Year	Associations found	Potential Biases	Comments
Gerdes 1995 95264241	Severe ROP: 1 dose: 47(16) 3 dose: 35(11) Physical evidence of CLD: 1 dose: 43(18) 3 dose: 40(15) Medication for CLD: 1 dose: 35(14) 3 dose: 30(11) Medication for chronic neurologic disease: 1 dose: 12(5) 3 dose: 3(1) Index<2 SD (%): 1 dose: 29(15) 3 dose: 30(13) Impairment present: 1 dose: 106(44) 3 dose: 92(35) No impair ment: 1 dose: 123(51) 3 dose: 155(59) Severity of impairment: Mild/moderate: 1 dose: 40(17) 3 dose: 39(15) Serious: 1 dose: 66(27) 3 dose: 53(20) Types of impairments: MDI<69: 1 dose: 40(16) 3 dose: 38(14) Moderate/severe CP: 1 dose: 22(9) 3 dose: 16(6) Bilateral sensorineural deafness: 1 dose: 5(2) 3 dose: 10(2) Deafness not requiring amplification: 1 dose: 5(2) 3 dose: 2(1) Bilateral blindness: 1 dose: 10(4) 3 dose: 4(2) Visual defect: 1 dose: 24(10) 3 dose: 22(8)	25% loss to follow up, equal in both groups 1 year follow up does not predict long term outcome from all infants	No data on funding source "Prenatal and postantal exclusion criteria were identical to those used in an earlier prophylactic trial of this synthetic surfactant" Died by 1-year adjusted age Lost to follow-up

Evidence Table 2. Randomized Controlled Trials for LBW Infants and Multiple Outcomes: CNS, Eye, Lung, Growth, etc.
Part III

Author, Year	Associations found				Potential Biases	Comments
O'Shea		*Dexamethasone*	*Placebo*	*P*	(None)	Study was government funded
1998	Definite Cerebral Palsy:	12	3			
98167528	Possible CP:	5	2			
98190123	Overall CP:	17	5	0.006		
	Neuro exam severe					
***also in CNS table**	Abnormal:	4	2			
	Mild abnormal:	16	6			
***overlapped sample as 98049056**	Overall abnormal					
	Neuro exam:	20	8	0.03		
	Authors analyze associations between prenatal factors and cerebral palsy in 80 infants with weights 500-1500g who were born in 1978-1989 to a resident of northwest region of Carolina. Factors that were strongly associated with increased risk of CP 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.					
O'Connor 2001 21376723	Growth (Wt, Ht, HC) no difference among the 4 pretem groups in terms of gm/kg/day for weight ; mm/wk for Ht and HC. Bayley at 12 months MDI range 92.2- 93.4 (no difference among 4 groups) PDI range 85.9-87.2 (no difference among 4 groups) For infants with BW<1250 gm Control group: PDI 81.8 which was sig less than PDI in AA-DHA (fish/fungal) (90.6)or AA-DHA (egg) (84.7) groups Language vocabulary comprehension at 14 mo. Comprehension: 97-101.6 (no difference among 4 groups) Production: 96.6-98.3 (no difference among 4 groups) Results support benefit in PDI of supplementing formulas for premature infants with AA+DHA from either fish/fungal or egg/fish source from first enteral feeding through 12 months in infants BW<1250 g				(None)	No data on funding source

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Leonard 1990 90204169	Location: US Years of Birth: 9/1/77- 9/1/82 Median GA (range), wk: 28.54±1.97 Mean BW (range), g: 1003±155 Male: 43% Race: ND Enrolled: 193 Evaluated: 129 Number of sites: 1	BW<1250 g Head CT between 5-6 days of life or head ultrasound days 3 and 10 after delivery	Died after discharge Lost to follow-up before reaching school age	VLBW infants (129): Without ICH (84), including 72 no parenting risk factor and 12 having parenting risk factor With ICH (45), including 38 no parenting risk factor and 7 having parenting risk factor	Prospective cohort (4.5 to 5 years)
Lucas 1992 92122860	Location: UK Years of Birth: 1982-1985 Mean GA: Sample 1: 31.4 ± 0.3 Sample 2: 31.4 ± 0.2 Mean BW: Sample 1: 1420 ± 30 Sample 2: 1440 ± 20 Males: Sample 1: 42% Sample 2: 55% Race: ND Enrolled: 313 Evaluated: 300 Number of sites: 5	Premature BW< 1850 g	ND	Sample 1: Preterms- no mother's milk (mother's choice not to provide breast milk to her infant within 72 hrs from delivery) [90] Sample 2: Preterms- mother's milk (mother's choice to provide breast milk to her infant within 72 hrs from delivery) matched with sample 1 for :BW, GA, need for ventilation, ds of NICU stay, other diets [210]	Prospective comparative longitudinal study (7.5-8 yrs)

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Robertson 1994 94181384	Location: Canada Years of Birth: 1990 Median GA (range), wk: ND Mean BW (range), g: 500-1500 Male: ND Race: ND Enrolled: 241 Evaluated: 163 ? 157 Number of sites: 2	BW 500-1249 g, lived born in Alberta to Alberta parents	Corrected rates exclude infants with syndromes and / or CNS malformations Survived to 1- and 2-years of corrected age	VLBW infants survived to 1 year corrected age (163) ? survived to 2 year corrected age (157)	Retrospective cohort (at 1 year and 2 year corrected age)
Spinillo 1994 94257064 ***sample overlaps with Spinillo, 1997**	Location: Italy Years of Birth: 1983-1989 Median GA (range), wk: Sample 1: 33.4±3.4 Sample 2: 31.6±4.3 Sample 3: 32.7±5.1 Controls: 32.7±4.0 Mean BW (range), g: Sample 1: 1800±458 Sample 2: 1641±570 Sample 3: 1768±633 Controls: 1748±569 Male: ND Race: ND Enrolled: 87 Evaluated: 77 (154 controls) Number of sites: 1	Cases: LBW infants with diagnosis of abnormal antepartum bleeding in mother's pregnancy Controls: two liveborn LBW infants of similar GA and free of malformations born immediately after each case	ND	Cases: Sample 1: Abruptio Placentae (40) Sample 2: Placenta Previa (22) Sample 3: Unclassified reason for antepartum bleeding (vaginal and cervical polyps, excessive blood show, and cervical lacerations) Controls (154)	Prospective cohort (2 year)

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Chen 1995 96009403	Location: Taiwan Years of Birth: 2/1990- 12/1991 Mean GA (range), wk: 30 (27-36) Mean BW (range), g: 1197 (625-1500) Male: ND Race: ND Enrolled: 74 Evaluated: 17 Number of sites: 1	VLBW preterm infants	ND	VLBW pretern infants (17): Group 1 - normal brain US (12) Group 2 - abnormal brain US (5, including 1 IVH grade I, 1 IVH grade III, and 3 PVL)	Prospective cohort (18-42 months) Left the hospital soon after birth at the request of their families (28) Families' refusal for further imaging studies (26 normal infants and 3 PVL infants)
Goetz 1995 96119489	Location: US Years of Birth: 1/1/1989 to 12/31/1992 Median GA (range), wk: ND Mean BW (range), g: 550-1100 Male: ND Race: ND Enrolled: 115 Evaluated: 14 Number of sites: 1	LBW < 1500 g Diagnosis of PVL	Death Transferred prior to being studied Not being followed-up	LBW infants with PVL (14)	Unclear (Retrospective or Prospective cohort, 11 months to 3 2/1 years)

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Speechley 1995 96356544	Location: Canada Years of Birth: 1978-1980 Mean GA: Sample 1: 37 (28-43) Sample 2: 40 (37-44) Mean BW: Sample 1: 2790 (850-4550) Sample 2: 3503 (2660-5170) Male: Sample 1: 56% Sample 2: 50% Race: Sample 1: whites : 90% Sample 2: whites: 90% (Original study: was a randomized interventional study of having a family volunteer visit the home on a regular base for 6 months) Eligible (for the original study): 828 Enrolled (for the original RCT): 312 Evaluated (at 12 yrs): 253 Number of sites: 1	All infants born at a tertiary care hospital in Ontario Born between 1978-1980 Transferred to NICU or Normal Neonatal Nursery (NNN)	Family residence more than 120 Km from hospital Newborn's survival was in question Language barrier Refused to participate to the original RCT.	Sample 1: Former NICU graduates: [116] Sample 2: Former NNN graduates [137]	Prospective, longitudinal, comparative, observational study (12 yrs)

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Wildin 1995 95385294 Wildin 1997 97422739 ***Data from same longitudinal study as Anderson, 1996 96314587 & Smith, 1996 97081985; overlapped sample**	Location: US Years of Birth: **1991-1992** Median GA (range), wk: Sample 1: 28.2±2.3 Sample 2: 30.8±2.2 Controls: 39.6±3.7 Median BW (range), g: Sample 1: 922±226 Sample 2: 1245±209 Controls: 3177±809 Male: Sample 1: 46% Sample 2: 42% Controls: 51% Race: African American Sample 1: 56% Sample 2: 56% Controls 3: 62% Enrolled: 370 Evaluated: 184 (114) Number of Setting: 2	(Sapme 1&2): BW< 1600g GA< 36wk Complete neurologic and developmental exams at 6 and 12 month corrected age. Controls: GA 37-42wks Apgar scores greater than 8 at 1 and 5 min Normal physical exam	"Significant" sensory impairment, meningitis, encephalitis, symptomatic congenital syphilis, congenital abnormality of brain, short bowel, HIV positive mother Primary care giver< 16y/o, drug abuser or did not speak English	Cases: preterm LBW infants (184): Sample 1: High risk (HR) (69) Sample 2: Low risk (LR) (115) Controls: Full Term (114)	Prospective cohort (at 6, and 12 months of age)

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Anderson 1996 96314587 Smith 1996 97081985 (CNS+All) ***Data from same longitudinal study (U. of Texas Health Sciences Center in Houston and the U. of Texas Medical Branch in Galveston) as Wildin, 1995 & 1997; overlapped sample**	Location: US Years of Birth: **1990-1992** Median GA (range), wk: Sample 1: 28.2±2.3 Sample 2: 30.8±2.2 Controls: 39.6±3.7 Mean BW (range), g: Sample 1: 922±226 Sample 2: 1245±209 Controls: 3177±809 Male: 50% Race: African American: Sample 1: 57% Sample 2: 62% Controls: 62% Caucasian: Sample 1: 25% Sample 2: 20% Controls: 25% Hispanic: Sample 1: 13% Sample 2: 15% Controls: 13% Other: Sample 1: 5% Sample 2: 3% Controls: 0% Enrolled: 368 Evaluated: 212 (128 controls) Number of sites: 2	(Sample 1&2): VLBW (<1600g) and GA<36 wk Female primary care giver completed both a 6 and 12 month home visit Controls: FT infants examined at 6 and 12 month corrected age	Infants with maternal substance abuse, major dysmorphisms, chromosomal anomalies, sensory impairment, meningitis, encephalitis, congenital syphilis, congenital abnormality of brain, cardiac abnormalities, NEC or HIV antibody positive Primary caregiver age < 16, drug abuser or not English-speaking (only in Smith, 1996)	Sample 1: High risk VLBW (89) Sample 2: Low risk VLBW (123) Controls: Full term (128)	Prospective cohort (6 and 12 months)

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Kato 1996 97182916	Location: Japan Years of Birth: 1984-1993 Median GA (range), wk: 28±2.8 Mean BW (range), g: 1031.3±271.7 Male: 48% Race: ND Enrolled: 305 Evaluated: 228 Number of sites: 2	VLBW singletons	Major anomaly Multiple gestation	VLBW infants (228)	Retrospective cohort (> 12 months)
Katz 1996 97145056	Location: UK Years of Birth: 5/83- 4/85 Median GA (range), wk: 29.2±2.5 (26-34) Mean BW (range), g: 1227.5±341.4 (740-2240) Male: Cases: 52% Controls: 55% Race: Cases: 75% White, 19% Black, 6% Asian Controls: 75% White, 12.5% Black, 12.5% Asian Enrolled: 212 Evaluated: 64 (40 controls) Number of sites: 2	≤34 weeks, no major congenital anomaly, 3 cranial u/s in first week of life	Lost to follow-up Too impair due to multiple cognitive, sensory, or motor disabilities, to complete testing	Cases: Preterm infants (64) Controls: Full-term comparison sample (40)	Prospective cohort (6-8 years)

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Korkman 1996 96374730 Psy1996	Location:Finland Years of Birth: ND Mean GA: Sample 1: 30.8 ± 2.25 Sample 2: 28.8 ± 1.41 Sample 3: 39.7 ± 1.98 Sample 4: 40.0 ± 0.77 Mean BW: Sample 1: 1068.5 ± 151.2 Sample 2: 1212.2 ± 189.3 Sample 3: 3596.7 ± 705.0 Sample 4: 3469.9 ± 275.9 Males: Sample 1: 44% Sample 2: 49% Sample 3: 42% Sample 4: 55% Race: ND Enrolled: ND Evaluated: 158 Number of sites: 2	Born at OB/GYN dept of Univ Helsinki F/up at Children's Hospital and Children's Castle Hospital Had neuropsychological assessment between 5yrs-9 yrs. And specifically for each sample: Sample 1: VLBW: less than 1500 g And SGA (at least 2 SD below mean for their GA) Sample 2: VLBW and AGA Sample 3: Asphyxiated Term infants, GA> 34 weeks with: Umbilical arterial ph<7.05 Or Apgar scores at 5 min less than 6 (From a Birth Cohort of 982 deliveries that included all the term asphyxiated infants) Sample 4: Healthy term with normal delivery, AGA (within 1.5 SD), Umbilical artery pH: 7.18 or more Apgar score 1 min: 8 or more Neonatal period: uneventful Born in the same hospital from healthy mothers by a singleton uncomplicated pregnancy	Children with : Cerebral Palsy Mental retardation Visual impairment	Sample 1: VLBW and SGA [34] Sample 2: VLBW and AGA [43] Sample 3: Birth asphyxia group of term infants [36] Sample 4: Control Group [45]	Prospective comparative longitudinal study (5-9 yrs) (mean age: sample 1: 7.1 yrs, sample 2: 7.3 yrs, sample 3: 6.9 yrs, sample 4: 6.11 yrs)

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Lucas 1996 96302121	Location: US Years of Birth: 1988- 1991 Median GA (range), wk: Sample 1: 29.8±0.2 Sample 2: 29.8±0.2 Mean BW (range), g: Sample 1: 1306±28 Sample 2: 1263±26 Male: Sample 1: 47% Sample 2: 47% Race: ND Enrolled: 275 Evaluated: 275 Number of sites: 2	Breast feeding BW<1850; GA< 37, Survived to randomization at 48-72 hr; Received any breast milk	Not resident in UK and the present major congenital abnormalities (e.g. trisomy) known to influence neurodevelopment	Sample 1: Fortified breast milk (137) Sample 2: Minimally supplemented breast milk (138)	RCT (9 and 18 months)

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Rieck 1996 Psy 1996 06905005	Location: Israel Years of Birth: ND Mean GA: ND Mean BW: ND Males: ND Race: Sample 1: whites 90%, asian-african10% Sample 2: whites: 94%, Asian-African: 5% Enrolled: Sample 1,2,3 : ND Evaluated: Sample 1: 103 Sample 2,3: ND Number of sites: ND	Sample 1: Premature VLBW < 1500 g Sample 2:: Children from middle socioeconomic class (MC) families Sample 3: Children from low socioeconomic class (LC) families	ND	Prospective longitudinal component: Sample 1: Premature VLBW <1500) [83] (mean age at assessment: 4.5 yrs) Cross-sectional comparative component: Sample 1 Premature VLBW < 1500 [83] Sample 2: Term children of middle class families [71] Matched with sample 1 only for mean age at assessment : 5.1 yrs Sample 3: Term children from low Class families [322] Matched with sample 1 only for mean age at assessment: 5.0 yrs	Longitudinal f/up study of children participating in a previous prospective longitudinal study (3-7 yrs) Cross sectional comparative component (3 arms: 2 control arms) (3- 7 yrs)

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Whitaker 1996 97040639	Location: US Years of Birth: 9/1/84-6/30/87 Median GA (range), wk: 31.5 Median BW (range), g: 1480.7 Male: 51% Race: White 74%, African-American 22%, Other 5% SES: middle class (19% of the families receiving public assistance) Enrolled: 685 Evaluated: 597 Number of sites: ND	BW 501-2000 g Survived to 6 years of age and participated in the study Home visit interview subjects	Families refusal (45) Unable to be located (143) Had been adopted (25)	Central New Jersey Neonatal Brain Hemorrhage study cohort LBW infants (597): Normal US finding (468) GM/IVH (83) PL/VE (46)	Prospective cohort (6 years)
Blitz 1997 97154301	Location: US Years of Birth: 1/90- 8/90 Mean GA (range), wk: 26.5±2.4 Mean BW (range), g: 775.9±138.4 Male: 36% Race: 40% White Enrolled: 248 Evaluated: 100 Number of sites: 1	Preemies, BW< 1001 g Maryland residents	Survived to hospital discharge Declined participation Serious congenital malformations, genetic disorder, diagnosed congenital syndromes with brain abnormality of known correlation with developmental disability, disorders secondary to prenatal toxic exposure with microcephaly, severe head injury after discharge Developed meningitis after discharge	ELBW preemies (100): Meningitis 6% PVL 10% Hydrocephalus 18% Seizures 7% IVH = grade III 26% BPD 63% ROP 49% Retinopathy of prematurity 49%	Prospective cohort

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Cheung 1997 97310950	Location: Canada Years of Birth: 1988-1993 Median GA (range), wk: 26 (24-30) Mean BW (range), g: 891 (530-1180) Male: 67% Race: ND Enrolled: 52 Evaluated: 21 Number of sites: 1	Preterm neonates (GA < 30 weeks, BW < 1200 g) with severe respiratory failure treated with high frequency ventilation (HFO)	ND	Preterms with IVH (21)	Retrospective cohort
Ekert 1997 97251211	Location: Canada Years of Birth: 1988-1994 Median GA (range), wk: 27.6±2.1 Mean BW (range), g: 962±262g Male: 50% Race: ND Enrolled: 123 Evaluated: 123 Number of sites: 2	GA<32 wks informed parental consent	Congenital anomalies, meningitis, congenital infections, GBS disease, lack of consent	Patients entering study (123)→ 104 left in analysis for outcome studies	Prospective cohort (seen at corrected age 4,8,12,18,24 months)

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Gerner 1997 97329414	Location: Sweden Years of birth: 1988-1993 Mean BW: 1047 ±258 g Mean GA: 28.2 ±2.7 wks Males: ND Race: ND Enrolled: Sample 1 and 2: 211 Sample 3: ND Evaluated: Sample 1: 50 Sample 2: 121 Sample 3: 35 Number of sites: 2	Sample 1 and 2: Premature,VLBW infants<15000g From NICU of Karolinska Hospital and St Goran's Hospital in Stockholm Born between 9/1988 and 2/1993. Inborns and outborns included Had neurodevelopmental assessment at 10 months corrected age Sample 3: Full term infants Uneventful pregnancy and delivery Apgar score at 5 min: 10 No neonatal complications Born at Karolinska hospital During the same period Matched with cases for: sex, maternal age, maternal education and parity Had neurodevelopmental assessment at 10 months corrected age	ND	Sample 1: Preterm VLBW infants "healthy" without any risk factors [50] Sample 2: Preterm VLBW infants With one or more risk factors [Brain hemorrhage, white matter lesion, surgical closure of PDA, ventilator treatment or septicemia (except Staph epi) [121] (Risk factors and group definition were based on the risk factors that were statistically significantly correlated with outcome in the cohort of the 171 preterm VLBW infants) Sample 3: Full term " healthy" infants, born at Karolinska hospital, during the same period, and matched with the combined preterm VLBW cohort [35]	First component: Prospective observational cohort with 171 preterm VLBW infants (sample 1 and 2) Second component: Prospective comparative component : sample 1 vs sample 3 Third component: Prospective Comparative component: Sample 2 vs sample 1 [10 months]

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Koller 1997 97193708	Location: US Years of Birth: 1975-1989 Median GA (range), wk: 30.9 (25-37) Mean BW (range), g: 117±227 Male: 45% Race: 51% Black Enrolled: 203 Evaluated: 203 Number of sites: 3	GA <1500, data obtained at 4 follow-up data points	ND	VLBW infants (203)	Retrospective cohort
Murphy 1997 97192793	Location: Korea Years of Birth: 1984-1990 Median GA (range), wk: Cases: 28.6±2.3 (24-32) Control: 29.9±1.9 (23-32) Median BW (range), g: ND Male: Cases: 63% Control: 57% Race: ND Enrolled: 638 Evaluated: 59 (234 controls) Number of sites: 1	GA<32 weeks Singleton Oxfordshire and West Berkshire resident Neonatal notes were available	Multiple birth Died before discharged	Cases: CP cases (59) Controls (234)	Case-control study

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Schendel 1997 98033417	Location: US Years of Birth: 12/1/89 to 3/31/91 Mean GA (range), wk: Sample 1: 28.4 ±3.0 Sample 2: 35.6 ±2.8 Controls: 39.4 ±1.5 Mean BW (range), g: Sample 1: 1088±268 Sample 2: 2184±267 Controls: 3417±432 Male: Sample 1: 49% Sample 2: 46% Controls: 52% Race: Black Sample 1: 37% Sample 2: 37% Controls: 41% Enrolled: 920 (555 controls) Evaluated: 920 (555) Number of sites: 5	Singleton livebirths in MMIHS study population, survived to 1 year of age Cases: MLBW infants, BW 1500-2499g; VLBW infants, BW<1500g Controls: NBW infants randomly selected from the birth certificate files on the basis of frequency matching with cases by maternal race, age, and residence	ND	Sample 1: VLBW infants (367) Sample 2: MLBW infants (553) Controls: NBW infants (555)	Case-control study
Thompson 1997 97268338	Location: US Years of Birth: : 1986-1991 Median GA (range), wk: 28.36±2.11(24-33) Mean BW (range), g: 1100±2.11 (700-1500) Male: 46% Race: ND Enrolled: 111 Evaluated: 55 Number of sites: 1	Born at Duke BW<1500g Survived to discharge or to 6 mo. corrected age	ND	VLBW infants (55)	Prospective cohort (4 years) Death (12), lost to follow-up (34), incomplete data (4), invalid score (5)

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Victorian Infant Collaborative study Group 1997 98026322 ***There are a series of Victorian articles in LBW-ALL. *This study will be combined in LBW-ALL table**	Location: Australia Years of Birth: 1979-80, 1985-87, 1991-92 Median GA (range), wk: ND Mean BW (range), g: ND Male: ND Race: ND Enrolled: 453 (242 controls) Evaluated: 448 (242) Number of sites: 3	(Sample 1-3): ELBW infants, BW 500-999 g born in Victoria, Australia Survived to age of 2 years Controls: Normal birth weight (>2499 g) infants born in 1991-1992	Excluded infants born in 1979-1980 for current review	Cases: ELBW infants (448): Sample 1: born in 1985-1987 (212) Sample 2: born in 1991-1992 (241) Controls: Normal BW (>2499 g) infants (242)	Retrospective cohort
Battin 1998 99002694	Location: British Columbia, Canada Enrollment period: 1991-1993 Mean GA: ND (range: 23-25 wks) Mean BW: ND (Mean BW for the 333 live births during the study period : for GA of 23 wks: 581, for GA of 24 wks: 648, for GA of 25 wks: 764) Male: ND Race: ND Enrolled: 333 (total live births GA: 23-28 wks) Evaluated : 44 (out of 49 of GA 23-25 surviving to NICU discharge) Number of sites: 2	Prospective cohort: Birth at British Children's Hospital and British Womens' Hospital Born during 1991-1993 Extremely low gestational age (ELGA): 23-25 wks Had follow up at 18 mo of age Historical control group: Born at the same institution Born between 1983-1989 GA: 23-25 wks	Cases of therapeutic termination of pregnancies for lethal congenital anomalies Outborns	Prospective cohort of ELGA born during a period when antenatal steroids, surfactant and dexamethasone for BPD had become an accepted treatment [44]	Prospective observational cohort study and a comparative study with an historical control group (18 months)

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Bos 1998 98218970	Location: Netherlands Years of Birth: 1992-1994 Mean GA (range), wk: 26-34 Mean BW (range), g: 835-1780 Male: ND Race: ND Enrolled: 27 Evaluated: 27 Number of sites: ND	AGA GA <35 wks Lived within 60km of hospital Normal US findings	Major congenital anomalies Developed cystic PVL, or grade 3 or 4 IVH	Preterm infants with echodensities (27)	Prospective cohort
Cherkes-Julkowski 1998 98262696	Location: ND Years of Birth: ND Mean GA (range), wk: ND Mean BW (range): Cases: 4.14±1.87 lbs Controls: 7.30±1.87 lbs Male: Cases: 61% Controls: 50% Race: ND SES: "middle class" Enrolled: 48 Evaluated: 28 (20 controls) Number of sites: 1	Preterm: <38 wks, BW<5 lbs, no congenital disorders, no retrolenteal fibroplasia, discharge from hospital prior to 42 wks conceptional age, mother willing to participate Controls: participants were enrolled in a longitudinal study before their second month of age	ND	Preterms (28) Controls: full term infants (20)	Retrospective cohort

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Emsley 1998 98238139 (CNS+ All)	Location: US Years of Birth: 1984 to 1994 Median GA (range), wk: Sample 1: 24.5 Sample 2: 24.2 Mean BW (range), g: Sample 1: 751.7 Sample 2: 697.1 Male: Sample 1: 67% Sample 2: 55% Race: ND Enrolled: 192 Evaluated: 64 Number of sites: 2	GA 23-25 weeks	Survived until discharge	Sample 1: Cohort 1 Born 1984-1989 (24) Sample 2: Cohort 2 born 1990-1994 (40)	Prospective cohort (3.3 –10.6 years)
Pasman 1998 98196839	Location: Netherlands Years of Birth: ND Median GA (range), wk: Sample 1: 28.9±1.5 (25-30) Sample 2: 32.5±1.1 (31-34) Sample 3: Sample 4: 30.1±1.6 (25-34) Controls: 39.4±1.5 (38-42) Mean BW (range), g: Sample 1: 1071±269 Sample 2: 1568±351 Sample 3: Sample 4: 1317±299 Controls: 3144±516 Male: ND Race: ND Enrolled: 81 (25 controls) Evaluated: 45 (18 controls) Number of sites: 2	GA=25-34 weeks, admitted to university hospital	Dysgenetic brain lesions Major congenital anomalies Clinical syndromes Lost to follow-up	Sample 1: Early preterms, low risk (15) Sample 2: Late preterms, low risk (21) Sample 3: Early high risk preterms (8) Sample 4: Late high risk preterms (9) Controls: Full term (18)	Prospective cohort (followed to 5-7 years age)

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Redline 1998 99086405	Location: US Years of Birth: 1983-1991 Median GA (range), wk: Sample 1: 27.3 ±2.3 Sample 2: 27.5 ± 2.2 Mean BW (range), g: Sample 1: 978± 228 Sample 2: 1012±226 Male: ND Race: African-American Sample 1: 57% Sample 2: 59% Enrolled: 72 Evaluated: 60 (59 controls) Number of sites: 2	Cases (Sample 1&2): Infants with major neurologic impairment at 20 months (strictly defined CP, loosely defined CP, hypertonia, Hypotonia) and those with NL neurologic exam at 20 months. Controls: infants born in the same year and matched for weight (±250 g), GA (±2 weeks), race, and sex who had a normal neurologic examination at 20 months.	No placental reports and slides available	Cases: VLBW infants with major neurologic impairment at 20 months (60) Sample 1: Strict CP (42) Sample 2: Neurologic abnormalities (18) Controls (59)	Case-control (at 20 months corrected age)
Rogers 1998 98438124	Location: US Years of Birth: 1988 to 1993 Median GA (range), wk: Sample 1: 27.9 ±2.0 Sample 2: 27.6 ±1.8 Mean BW (range), g: Sample 1: 1158±330 Sample 2: 1082± 290 Male: ND Race: ND Enrolled: 41 Evaluated: 41 Number of sites: 1	GA < 33 weeks live birth with unspecified IVH	ND	Sample 1: No growth failure (23) Sample 2: Growth failure (18)	Retrospective cohort

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Spinillo 1998 98237382 Spinillo, 1997 98021316 & 97277958 ***have some overlapped sample with spinillo, 1994**	Location: Italy Years of Birth: 1987 to 1993 Median GA (range), wk: Cases: 29.6 Controls: 30.5 Mean BW (range), g: Cases: 1317 Controls: 1451 Male: 52% Race: ND Enrolled: 461 Evaluated: 345 Number of sites: 2	GA 24–33 completed weeks Had a US scan done before 20 weeks' gestation	Severe malformations or chromosome abnormalities	Sample 1: Preterm infants with CP (40) Sample 2: Preterm infants without CP (305)	Prospective cohort (3, 6, 12, and 24 months)
Tin 1998 99046171	Location: North of England Years of Birth: 1983, 1990-1991 Median GA (range), wk: ND Mean BW (range), g: ND Male: ND Race: ND Enrolled: 1983 (230); 1990-1 (566) Evaluated: 1983 (230); 1990-1 (566) Number of sites: 5	GA 23-31 weeks	ND	1983 cohort (230): Child reviewed without difficulty (204) Child traced with difficulty (14) Child seen with difficulty after child was traced (12) 1990 to 1991 (566): Child reviewed without difficulty (505) Child traced with difficulty (26) Child seen with difficulty after child was traced (35)	Prospective cohort *2 Cohorts of different time periods

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Burguet 1999 99126269	Location: France Years of Birth: : 10/1/90- 9/10/92 Mean GA (range), wk: 25-32 Mean BW (range), g: 8% BW>2000g Male: 51% Race: 86% Caucasian SES: 5% Family precariousness Enrolled: 203 Evaluated: 167 Number of sites: 20	All liveborn premature in 20 maternity hospitals in Franche-Comte region	Chromosomal or neurological congenital anomaly diagnosed in the neonatal period, discordance of 2 wks or more between pediatric and obstetrical or echographic determination of gestational age, triplets and more	Preemies (167): RDS 40% No RDS 60%	Prospective (93%) and retrospective (7%) cohort (followed until 2 years of age)
Cooke 1999 99257637	Location: UK Years of Birth: 1982-1993 Median GA (range), wk: ND Mean BW (range), g: ND Male: ND Race: ND Enrolled: 1722 Evaluated: 1187 Number of sites: 1	VLBW (not specifically defined) Have data at 3 years old	ND	VLBW infants (1187): 1982-19855 (411) 1986-1989 (387) 1990-1993 (398)	Retrospective cohort (followed until 3 years corrected age)
Cooke 1999 99380719	Location: UK Years of Birth: 1982-1993 Median GA (range), wk: 28.6±1.7 (24-35) Mean BW (range), g: 1103±203 (630-1500) Male: ND Race: ND Enrolled: 137 Evaluated: 87 (8 controls) Number of sites: 1	VLBW infants prospectively followed birth to age 13 with MRIs between age 15-17 yrs Controls: FT infants	ND	VLBW infants (87), with white matter disorder, PVL, Ventriculomegaly, MRI abnormality Controls: FT infants (8)	Prospectively cohort (15-17 years)

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Finer 1999 99436635	Location: UK Years of Birth: 1/1/94 to 12/31/96 Median GA (range), wk: 25 (24-28) Mean BW (range), g: 663 (440-968) Male: 50% Race: ND Enrolled: 177 Evaluated: 10 (10 controls) Number of sites: 1	Cases: Inborn infants BW < 1000g Received DR-CPR Survived until discharge Controls: Matched controls with similar mean BW and length of follow-up	Lethal congenital malformations	Cases: ELBW survived infants received DR-CPR (10) Controls (10)	Retrospective cohort (median 28 months)
Futagi 1999 99450356	Location: Japan Years of Birth: 1981-1986 and 1989 1993 Mean GA: Sample 1: 27.2±2.2 Sample 2: 26.8±2.4 Mean BW: Sample 1: 834.1±133.4 Sample 2: 786.0±133.2 Males: Sample 1: 38% Sample 2: 53% Race: ND Enrolled: 305 Evaluated: 276 Number of sites: 1	Presurfactant era cohort: BW less than 1000 gms Admitted to NICU Born during presurfactant era 1981-1986 Follow up for at least 3 years. Neurodevelopmental and Mental outcome documented in medical records Surfactant era cohort: same as above except Born during surfactant era, 1989-1993	Hereditary disorders Chromosomal abnormalities Follow up less than 3 years Absence of documentation of neurodevelopmental or mental outcome in medical records	Sample 1 Presurfactant cohort: Born during presurfactant era, between 1981-86 [107] Sample 2: Surfactant era cohort: Born during surfactant era, between 1989-1993 [169]	Retrospective comparative longitudinal study. Comparison done between 2 retrospective cohorts (pre-surfactant era cohort vs surfactant era cohort) [3-8.8 years, mean f/up: 6.0 ±1.3 yrs (not given per group)]

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Kim 1999 99416608	Location: UK Years of Birth: July 1996 to November 1997 Median GA (range), wk: Cases: 30.8±3.5 Control: 31.4± 2.2 Mean BW (range), g: Cases: 1557±252 Control: 1418±376 Male: Cases: 47% Control: 52% Race: ND Enrolled: 184 Evaluated: 17 (62 controls) Number of sites: ND	Preterm (GA<37 wks) infants and term infants with an Apgar score of less than 6 at 5 minutes, neonatal hyperbilirubinemia (total bilirubin concentration of 20 mg/dl or more) and bacterial meningitis BW<2000 g	Chromosomal abnormalities and congenital malformation	Cases: VLBW infants with CP or Developmental D (17) VLBW Controls (62)	Prospective cohort (at 2, 6, 12 months corrected age)
Krageloh-Mann 1999 99431017	Location: Denmark Years of Birth: 1986- 1989 Median GA (range), wk: 30.2 (27-34) Mean BW (range), g: 1461 (690-2655) Male: 66% Race: ND Enrolled: 40 Evaluated: 29 (57 controls) Number of sites:1	Preterm infants	Death (1), lost to follow-up (7), parental refusal (4), difficulties with sedation for MRI (1)	Cases: preterm infants (29) Controls: term-born pre-school children (57)	Prospective cohort

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Salokorpi 1999 99353226	Location: Finland Years of Birth: 1991 to 1994 Median GA (range), wk: Sample 1: 26.7 ±2.0 Sample 2: 26.7 ±2.4 Mean BW (range), g: Sample 1: 833±130 Sample 2: 817± 130 Male: Sample 1: 33% Sample 2: 46% Race: ND Enrolled: 228 Evaluated: 143 Number of sites: 1	Premature infants, BW < 1000 g, admitted to NICU	ND	Sample 1: CP present (27) Sample 2: CP absence (116)	Prospective cohort Lost to follow-up (13) due to parent refusal or because had moved to remote areas Died by the age of 2 year (72)
Shepherd 1999 99165413	Location: Scotland Years of Birth: 2/95 to 2/97 Median GA (range), wk: 25.7-35 Mean BW (range), g: 570-3200 Male: ND Race: ND Enrolled: 81 (68 controls) Evaluated: 81 (68) Number of sites: 1	Preterm infants admitted to the special-care unit	Genetic or prenatal anomalies	Cases: preterms (81) Controls: term infants (68)	Prospective cohort

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Stathis 1999 99325758	Location: Australia Years of Birth: :1977-1986 Median GA (range), wk: 27.7(27.3-28.1) Mean BW (range), g: 860 (837-833) Male: 36% Race: ND Enrolled: 124 Evaluated: 87 Number of sites: 1	BW 500-999g survived to discharge Cared for in study NICU Enrolled in follow-up programs	ND	ELBW survived infants (87)	Prospective cohort (followed at 4, 8, 12, months)
Vohr 1999 99332101	Location: US Years of Birth: 1989-1992 Median GA (range), wk: Sample 1: 27.9±2 Sample 2: 28±2 Mean BW (range), g: Sample 1: 960±178 Sample 2: 965±179 Male: Sample 1: 59% Sample 2: 56% Race: Sample 1: Black 21%, Hispanic 3%, White 76% Sample 2: Black 20%, White 78%, Other 2% Enrolled: 392 Evaluated: 278 Number of sites: 3	BW 600-1250g Survived the first 3 years of life, and were seen for neurodevelopmental follow-up at 36 months CA	Non-English speaking home	Sample 1: Early IVH positive (29) Sample 2: Early IVH negative (249)	Unclear (Retrospective or prospective cohort, followed to 36 months corrected age)

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Agustines 2000 20279724	Location: US Years of Birth: 1990-1995 Median GA (range), wk: 25 (24-29) Median BW (range), g: 674 Male: ND Race: ND Enrolled: 63 Evaluated: 36 Number of sites: 1	BW: 500-750 g Born in Long Beach Hospital, between 1990 and 1995 (post corticosteroid, postsurfactant era) Survived to discharge Had follow up at 30 months	ND	VLBW infants (36)	Retrospective cohort (followed to 30 months CA) Lost to follow-up (27)
Breslau 2000 20298367	Location: US Years of Birth: 1983-1985 Mean GA (range), wk: ND Mean BW (range), g: ND Male: ND Male: ND Race: Sample 1 (urban) Blacks: 80% Sample 1 (suburban) Blacks:11% Sample 2 (urban) Blacks:74% Sample 2 (suburban) Blacks: 3% Enrolled: 1095 Evaluated: 823→717 Number of sites: ND	LBW cohort: <2500 g NBW cohort: Born between 1983-85, that were 6 yrs old during 1990-92; when the fieldwork took place From 2 major hospitals of South Michigan: one urban and one suburban (In each hospital, random samples of LBW and NBW children were drawn).	From the target sample: were excluded children with severe neurologic impairment: CP, MR, blindness From the analysis of incidence of severe attention problems were excluded children that already had severe attention problems at the assessment at 6 yrs	At 11 yrs (717): Sample 1: LBW (411) – Urban LBW (217) Suburban LBW (194) Sample 2: NBW (306) - Urban NBW)164) Suburban NBW (142)	Prospective cohort (11 years)
Buhrer 2000 20280896	Location: Germany Years of Birth: 1/192- 12/31/97 Mean GA (range), wk: 28.7 (23.2-37.2) Mean BW (range), g: 1149 (430-1495) Male: ND Race: ND Enrolled: 455 Evaluated: 352 Number of sites: 1	VLBW, BW < 1500 g	ND	VLBW infants (352)	Prospective cohort (followed until 1 year CA)

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Grether 2000 20448692	Location: US Years of Birth: 1988-1994 Median GA (range), wk: Cases: : 27.1±2.4 Controls: 37.6±2.6 Mean BW (range), g: Cases: 1085±350 Controls: 1112±349 Male: Cases: 56% Controls: 47% Race: Cases: 47% White Controls: 33% White Enrolled: 170 (280 controls) Evaluated: 170 (280) Number of sites: 22	BW < 1500g or BW 1500-1999g and <33 GA	Postural cause of CP identified. Congenital infection identified	Cases: Cerebral palsy (170) Controls (288)	Retrospective case-control study (2 years)
Katz-Salamon 2000 20332284	Location: Sweden Years of Birth: 1988-1993 Median GA (range), wk: Cases: : 26.1±2.0 Controls: 26.7±1.3 Mean BW (range), g: Cases: 874±183 Controls: 940±179 Male: ND Race: ND Enrolled: 70 Evaluated: 43 (43 controls) Number of sites: 1	Cases: VLBW Survival with CLD Controls: No IVH>2 No CLD No PVL VLBW	Cases: Unable to be examined because of other medical problems, including congenital cardiac malformation, hepatitis C, immobilization of the legs, severe visual defect, and severe cerebra infarction.	Cases: VLBW infants with CLD (43) VLBW Controls (43)	Prospective cohort

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Marlow 2000 20150342	Location: UK Years of Birth: 1990-1994 Mean GA: ND (Median and Range) Sample 1: 28 (26-31) Sample 2: 28 (26-31) Mean BW: ND (Median and range) Sample 1: 960 (600-2914) Sample 2: 1026 (410-2814) Male: ND Race: ND Enrolled : 27 Evaluated: 15 Number of sites: 1	For sensorineural hearing loss (SNHL) group GA: <33 wks Family resident of Greater Bristol area Records at Hearing Assessment Center of Royal Hospital for Sick children. Born during 1990-1994 Diagnosis of SNHL of 50 dB For control group: Matched controls 2:1 to cases Admitted to the same NICUs as cases Matched for sex and GA and next and preceding matching children in the admission books of St Michael's and Sothmead hospitals	ND	Sample 1: SNHL group [15] Sample 2: Control group [30] Matched with cases for sex, GA, admission dates in NICU	Retrospective case control study with a longitudinal component (unclear if retrospective or prospective) (12 mo CA)
Palta 2000 20096107 (CNS+Eye)	Location: US Years of Birth: August 1988-June 1999 Median GA (range), wk: 28.54±1.97 Mean BW (range), g: 1003±155 Male: 43% Race: ND Enrolled: 626 Evaluated: 425 Number of sites: 6	Birth weight =1500 g Survived to 5 years of age Parental agreement to potential follow-up and provided recontact information before discharge.	Refusing participation at follow-up	VLBW infants (425)	Prospective cohort (followed to an average age of 5 years)

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Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Torrioli 2000 20275419 (CNS+Eye)	Location: Italy Years of Birth: 1991-1993 Median GA (range), wk: 32 (21-34) Median BW (range), g: 1120(560-1500) Male: 42% Race: ND SES: "medium and there was the same ethnic background" Enrolled: 86 Evaluated: 36 (ND on number of controls) Number of sites: 1	BW < 1500 gm Controls: born at term and without any perinatal or neonatal complication, matched for age, gender and socioeconomic condition including occupational status of the family and parents' educational status was performed by the same observers that examined the study group	Frankly disabling conditions (CP, MR, blindness, CNS infections, genetic syndromes, etc.); abnormal head ultrasound findings Refused to participate in the study	VLBW preterm infants (36)	Prospective cohort
Valkama 2000 20233239	Location: Finland Years of Birth: 11/1/1993-10/31/1995 Median GA (range), wk: 29.3±2.2 (24.9-33.7) Median BW (range), g: 1153±289 Male: 53% Race: ND Enrolled: 62 Evaluated: 51 Number of sites: 1	VLBW<1500g and <34 weeks	Congenital anomalies Died during neonatal period Parental refusal	VLBW preterm infants (51)	Prospective cohort (18 months)

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Vohr 2000 20295211	Location: US Years of Birth: 1/93-12/94 Median GA (range), wk: Mean BW (range), g: Male: Race: Enrolled: Evaluated: Number of sites: 12	Live born BW 401-1000 g	ND	1151 extremely low birth weight survivors cared for in the 12 participating centers of the National Institute of Child Health and Human Development Neonatal Research Network	Prospective cohort (18-22 months corrected age)
Dammann 2001 21334215	Location: Germany Years of Birth: July 1983-June 1986 Median GA (range), wk: ND Mean BW (range), g: ND Male: ND Race: ND Enrolled: 591 Evaluated: 324 Number of sites: 1	BW≤1500g	ND	LBW infants (324): SGA (92) AGA (232)	Prospective cohort (6 years) 7 non-BSCP cerebral palsy (no further explanation)

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Gaillard 2001 21221175	Location: UK Years of Birth:1994-1996 Mean GA: ND (only median and range given) Sample 1: 26 (23-34) Sample 2: 26 (23-33) Mean BW: ND (only median and range given) Sample 1: 852 (520-2710) Sample 2: 745 (580-1620) Male: Sample 1: 57% Sample 2: 50% Race: ND Enrolled: 100 Evaluated: 84 Number of sites: 1	Retrospective cohort : All infants born from 1/1/1994 to 12/31/1996 Born at Liverpool Women's Hospital Ventilated beyond 27 postnatal days	If transferred from another hospital after first postnatal week (mostly surgical referrals) If ventilated after 27 postnatal days after a surgical procedure requiring anesthesia	Sample 1 : Ventilated beyond 27 (but not 50) postnatal ds (56) Sample 2: Ventilated beyond 49ds (28)	First component: Retrospective longitudinal cohort with case-control design and cases defined based on exposure (length of ventilation). Unmatched. (3 years) Second component: Retrospective longitudinal cohort study With two historical control groups (3 years)
Horwood 2001 20574647	Location: US Years of Birth: 1/93 to 12/96 Median GA (range), wk: ND Mean BW (range), g: ND Male: ND Race: ND Enrolled: 413 Evaluated: 298 Number of sites: 1	VLBW infants admitted to neonatal unit still living in New Zealand at time of assessment, 7-8 years of age	Death 17 children could not complete IQ testing because of substantial disability	VLBW infants (298)	Prospective cohort

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Nadeau 2001 21163667	Location: Canada Years of Birth: 1987-1990 Median GA (range), wk: Cases: 27.4±1.1 Control: 39.8±1.6 Median BW (range), g: Cases: 1024.3±204.2 Control: 3453.4±497.8 Male: Cases: 51% Control: 50% Race: ND Enrolled: 129 Evaluated: 86 ? 61 (50 controls) Number of sites: 1	Cases: GA<29 weeks, BW<1500 g Controls: Normal BW children , born at the same hospital during the same time period	Cases: Lost to follow-up at 5 years 9 months: families had moved away (33), parents' refusal (10) Lost to follow-up at age 7: families had moved away (10), parents' or school's refusal (13)	Cases: EP/VLBW infants (86? 61)	Prospective cohort (at 18 months, 5 years 9 months, and age 7)
Pierrat 2001 27221167	Location: France, Netherlands Years of Birth: 1990-1998 Median GA (range), wk: 28.54±1.97 Mean BW (range), g: 1003±155 Male: 43% Race: ND Enrolled: 72 Evaluated: 60 (59 controls) Number of sites: 2	GA < 32 weeks, admitted to Lille and Utrecht Diagnosis of grade II or III PVL	ND	Preterm infants with PVL (78): Grade II (39) Grade III (39)	Prospective cohort (1 year) Cysts on the first scan and therefore were considered to be of antenatal onset (7), admitted after the first month of life with evidence of cysts on the first scan (9); no definite classification could be achieved (2)

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Leonard 1990 90204169	*CNS Predictors:* Intracranial/ Intraventricular hemorrhage *Cardiovascular or Pulmonary Predictors:* Number of days on supplemental oxygen to help $pO_2 > 50$ *Other predictors:* Parenting risk factor Low socioeconomic status	Intracranial/ Intraventricular hemorrhage - Grades 0-IV by Papille; head CT if born before 1981, head U/S is born after 1981 Parenting risk factor - defined as referral by a physician, nurse, or health professional to child protective services for neglect or mild abuse (none were for severe abuse) Low socioeconomic status - one or both parents unemployed, mother not complete high school or health insurance through public assistance	**CNS:** Neurodevelopmental: 1) Cognitive delay 2) Neurologic abnormalities	Cognitive delay: measured by McCarthy Scales of Chilren's Abilities, Wechsler Intelligence Scale for Children (Revised), Wechsler Preschool and Primary Scale of Intelligence, and Stanford-Binet "mild" - score between 1-2 SD below the mean (69-83) "moderate to severe" - score >2 SD below the mean Neurologic abnormalities: abnormalities in muscle strength, tone, reflexes or movement that cause functional impairment, i.e. hemiplegia, ataxia, quadriplegia. Clumsiness or mild tremors not included.
Lucas 1992 92122860	Primary predictor: General: 1) Maternal choice to breast feed Secondary predictors: Others: 1) Received mother's milk 2) Social class 3) Maternal education 4) Gender 5) Days of ventilation	Social class: 4 categories: • Social class I or II • Non manual Social class III • Manual social class III • Social class IV or V Mother's education: 5 point scale From 1: no educational qualifications To 5: degree or higher performance qualifications	IQ score in Weschler Intelligence Scale for Children-Revised-Shortened version (WISC-R)-Anglicised. 1) Verbal scale 2) Performance scale 3) Overall IQ (Assessment at 9 mo, 18 mo, 7.5-8 yrs)	Not further specified

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Robertson 1994 94181384	Birth weight	ND	**CNS:** CP Neurodevelopmental: Motor delay Seizure disorder Multiple disabled **Ophthalmology**: Visual **Audiology**: Hearing	CP definition was that of Bax, "A disorder of movement and posture due to a defect or lesion of the immature brain", along with more recent guidelines by Levine using at least four of six clinical motor abnormalities leading to a constellation of findings of the cerebra palsy syndrome Mental retardation = scores Bayley mental scales. Initially by newborm screening; with subsequently tested repeatedly in a sound booth and/or by bristem audiological evoked response. Visual loss: acuity in the best seeing eye after correction, <20/60) including legal blindness (corrected acuity, <20/200) Hearing loss (loss of >= 30 dB binaurally)
Spinillo 1994 94257064 ***have some overlapped sample with spinillo, 1997**	Cause of antepartum bleeding CNS: Intracranial hemorrhage Periventricular leukolacia	Histological examination of deta ched placeta were used for confirmation of clinical classification Diagnosis of IVH and PVL according to US finding	**CNS:** CP Neurodevelopmental: Motor and cognitive delay Mental retardation Presence of grade 3-4 IVH or PVL	Amiel-Tison and Grenier Neonatal neurological Examination Major neonatal handicaps included definite CP such as spastic diplegia, hemiplegia or tetraplegia causing definite physical disability with moderate to severe interference with functioning, or mental retardation (Bayley Scale)

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Chen 1995 96009403	CNS: 1) Intracranial hemorrhage 2) Periventricular leukomalacia	ND	**CNS**: Motor delay CP	Development Screening test, modified for Chinese children Diagnosed by "complete neurological exams", including transient spasticity and spastic di-/ quardriplegia
Goetz 1995 96119489	PVL	ND	**CNS:** CP Neurodevelopmental: Motor and cognitive delay Seizure disorder **Ophthalmology:** Visual impairment	ND

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Speechley 1995 96356544	General: 1) Former NICU graduate (of any BW) 2) Gender	Not further specified	Physical health outcome at 12 yrs 1) Chronic physical health (mother's report) 2) Lifetime hospitalizations (mother's report) 3) Physical impairments (mother's report) 4) Perception of child's heath (child's report) 5) Perception of child's health (mother's report) Emotional and social well being at 12 yrs: 1) Internalizing problems (child's report) 2) Externalizing problems (child's report) 3) Social competence (child's report) 4) Social support (child's report) 5) Self esteem (child's report) 6) School performance (mother's report)	Based on responses on an interviewer administered and self-report questionnaire. Physical health outcome at 12 yrs 1) Chronic physical health (mother's report): Precoded 25 chronic illnesses 2) Lifetime hospitalizations (mother's report) 3) Physical impairments (mother's report):response to a question asking whether their child had any physical impairments 4) Perception of child's heath (child's report): 4-item scale 5) Perception of child's health (mother's report): 4-item scale Emotional and social well being at 12 yrs: 1) Internalizing problems (child's report) 3-item scale 2) Externalizing problems (child's report) 3-item scale 3) Social competence (child's report) 36-item scale 4) Social support (child's report) 24-item scale 5) Self esteem (child's report) 10-item scale 6) School performance (mother's report) 5-item scale

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Wildin 1995 95385294 Wildin 1997 97422739 ***Data from same longitudinal study as Anderson, 1996 96314587 & Smith, 1996 97081985; overlapped sample**	CNS: 1) Neurological exam- 6 months - 12 months 2) Quantitative neurologic score Other: 1) Socioeconomic status 2) Medical risk category: High Risk (HR); Low Risk (LR)	Based on Amiel-Tison examination done at 6 months corrected age High medical risk = severe medical complications of prematurity	**CNS:** Neurodevelopmental: Motor delay Cognitive delay Rate of development	Stanford-Binet developmental test McCarthy Gross Motor subtests Bayley scale

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Anderson 1996 96314587 Smith 1996 97081985 (CNS+All) ***Data from same longitudinal study (U. of Texas Health Sciences Center in Houston and the U. of Texas Medical Branch in Galveston) as Wildin, 1995 & 1997; overlapped sample**	Other Predictors: Illness Acuity – grouped into low-risk and high-risk. Maternal Behaviors: 1) warm sensitivity 2) Maintaining of infant interests and directiveness.	Based on the severity of neonatoal complications grouping into High- and Low- risk groups: High risk: =1 severe neonatoal complications, including chronic lung disease (bronchopulmonary dysplasia), grade III or IV intraventricular hemorrhage, and periventicular leukomalacia Low risk: : =1 less severe neonatal complications, including transient respiratory distress, respiratory distress syndrome, and grade I or II intraventricular hemorrhage, and periventicular leukomalacia Maternal Behaviors - home observation with use of a rating scale.	**CNS:** Neurodevelopmental: Cognitive delay **Audiology**: Language **Other**: Living skills	Baley Mental and Psychomotor development indices (MDI, PDI) Neurologic scores based on scales developed by Amiel-Tison, Baird and Gordon, and Swaiman Sequenced mixture of communication development Daily living skills subscale from Adaptive Behavior Scale
Kato 1996 97182916	VLBW GA Sex Perinatal factors (mat age, parity, preeclampsia, previa, PROM, fetal presentation,	VLBW= ND Small for Dates = ND PROM = ND	**CNS** *CP:* Neurodevelopmental: Mental retardation Seizure disorder Blindness Lump all together as major handicap	ND

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Katz 1996 97145056	General: GA CNS: 1) Intracranial/ Intraventicular hemorrhage 2) Periventricular leukomalcia (cystic PVD) 3) PVD (if unilateral or bilateral periventicular echogenic lesions present on at least 3 scans)	IA IVH: no lesion= consistently NC scans. Mild lesion = germinal hem or small IVH or PVD or mild vent dilation without hem. Severe lesion: blood distends the vents or in parenchyma, or multicystic PVC.	**CNS:** Neurodevelopmental: Attention IQ	 Measured by CPT test (continuous Performance Test) measuring errors of omission or commission. Is also measured by CBCC (Child Behavior Check List): parents check off behavior related to n attention and hyperactivity. Measured by British Abilities Scale
Korkman 1996 96374730 Psy1996	Main predictors: General: 1) VLBW and AGA (surrogate for perinatal asphyxia in preterm) 2) VLBW and SGA (surrogate for ante-natal asphyxia in preterm) Secondary predictors General: 1) Apgar scores 2) Arterial PH at 2 hrs of life 3) Intrauterine growth retardation 4) BW Pulmonary: 1) RDS 2) Duration of ventilatory tx CNS: 1) IVH	1) 2) VLBW: less than 1500 g 3) SGA: 2 SD below normal for GA 4) Birth asphyxia: Umbilical arterial ph<7.05 5) Or Apgar scores at 5 min less than 6	1) 2) Psychometric Intelligence score. 3) Detailed Neuropsychological assessment score. 4) Neurological Disability status examination (Assessment between 5-9 yrs)	Psychometric Intelligence score: by Finnish standardized Revised version of the Wechsler Intelligence Scale for Children (WISC-R 1984) 1) FSIQ: Full Scale IQ 2) VIQ: Verbal IQ 3) PIQ: performance IQ Detailed Neuropsychological assessment score: 1) NEPSY test (a new test consisting of testing of attention, language, motor, sensory, visuospatial and memory subsets) 2) The Token te st shortened version 3) The VMI test Established Finnish norms. Scores reported as SD scores (z scores) Sum scores in all 3 tests also calculated Neurological Disability status assessment: not specified

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Lucas 1996 96302121	General: 1) Full fortification for breast milk	Full breast milk Fortification vs Minim supplementation with minerals only, both groups received vitamins	**CNS:** 1) Neurodevelopmental: 2) Motor delay 3) Mental retardation **Audiology:** 1) Language **Other:** 2) Social development	At 9 month: Knobloch Developmental Inventory At 18 month: Knobloch; Bayley scales; Vineland test of social maturity

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Rieck 1996 Psy 1996 06905005	In prospective longitudinal component: General: 1) Perinatal factors: 2) BW 3) GA 4) SGA 5) Neurological complications in NICU 6) Sex Growth: 1) HC percentile CNS: 1) Developmental scores at 1-2 yrs of age Others: 1) Age at assessment 2) Parental (mother's and father's) age 3) Parental education 4) Country of origin Prospective comparative component. • VLBW vs Middle class term child And vs Low class term child	Neurologic complications in NICU: 1) Severe asphyxia 2) Loss of consciousness 3) Convulsions 4) IVH grade 3-4 5) CNS infections HC percentile: 1) > 20% 2) 3-20% 3) < 3% Country of origin: Israel Euro-American Asian-African	**CNS:** Neurodevelopmental outcome: 1) Scores in McCarthy 's 5 Scales of Children's Abilities test (MSCA) 2) General Cognitive Index (GCI) score (Assessment between 3-7 yrs of age)	MSCA: Translated in Hebrew Adapted to Israeli children 5 scales: 1) Verbal 2) Perceptual-Performance 3) Quantitative 4) Memory 5) Motor (GCI) scores: From subtests of the : 1) Verbal 2) Perceptual-performance and 3) Quantitative scales

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Whitaker 1996 97040639	General predictors: BW,GA, SGA/IUGR Chronic illness, Apgar score Sex CNS Predictor: IVH PL/VE Bronchopulmonary dysplasia Maternal-social disadvantage	Mat-Social Disadvantage: not high school gradated; nonwhite race; income from public assist; <19 yrs; not married. According to US findings	**CNS**: Neurodevelopmental: Cognitive delay Mental retardation Memory **Ophthalmology** : Visual perceptual **Audiology:** Language	 Test of language Development Stanford-Binet Intelligence Scale
Blitz 1997 97154301	Neonatal complications of ELBW infants, including meningitis, PVL, hydrocephalus, seizures, IVH, BPD, ROP, and whether the infant was discharged on oxygen	Diagnosis based on hospital course. IVH = grade III	**CNS:** CP Neurodevelopmental Development outcome Neurologic Outcome **Ophthalmology:** Visual problems **Audiology:** Hearing loss Hearing loss Visual problem	BSID (Bayley Scale of Infant Development), MDI (Mental Developmental Index), PDI (Psychomotor developmental Index), CLAM (Clinical Linguisitc and Auditory Milestone Scale): Total (CLAM-T), Expressive (CLAM-E), and Receptive (CLAM-R) scores Neurodevelopmental examination, modified after Amiel –Tison and the Primitive Reflex Profile ND Strabismus, hyperopia, myopia, or retinal detachment
Cheung 1997 97310950	IVH grade III or IV	Diagnosed by US finding	**CNS:** Cognitive delay	Cognitive delay - Belay Mental and Psychomotor development indices (MDI, PDI) Normal neurodeveloplement: free of neurodevelopmental disability, with Bayley scores higher than 2 SD below the mean Neurodevelopmental disability: cerebral palsy or blindness or hearing loss

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Ekert 1997 97251211	General: 1) Birth weight 2) GA 3) Apgar score CNS: 1) Intracranial / Intraventricular hemorrhage 2) Periventricular leuko-malacia Cardiovascular/pulmonary: 1) Bronchopulmonary dysplasia other: a) ventilator days, b) 02 days Other: Hospital/health care resource (admission days) utilization.	Diagnosis of IVE or PVE according to US findings	**CNS:** Motor delay Cerebral palsy Cognitive delay	Motor and cognitive delays: Bayley score of < 84 (i.e., =1 SD below mean) or developmental quotient (developmental age divides by corrected age) of < 0.75 Evidence of hypertonicity and hyperreflexive in association with at least gross motor developmental delay

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Gerner 1997 97329414	General: 1) Prematurity (per se) 2) General maternal, obstetric, and perinatal predictors: ➢ Maternal education ➢ Maternal age ➢ Parity ➢ Maternal toxemia ➢ Maternal septicemia ➢ Placental bleeding ➢ Sex, Gestational age, Birth weight, Intrauterine growth, Cardiotocography, Apgar score at 5 min 3) CNS: (Ultrasound findings) ➢ Subependimal bleeding ➢ Intraparenchymal lesions 4) Cardiovascular or Pulmonary: ➢ PDA, RDS, Surfactant therapy, Days of Ventilatory tx, Chronic Lung Disease (CLD), Pneumothorax, 5) Other : ➢ Age at time of test, Infantile septicemia.	Maternal education:3 levels Parity: 0 or more Maternal toxemia, Maternal septicemia, Placental bleeding: presence or absence Intrauterine growth: SGA or AGA Cardiotocography: normal or abnormal All cranial U/S findings classified according to the most advanced stage observed Subependymal bleeding: 3 grades: B1: isolated germinal matrix/ subependymal haemorrhage B2:IVH without ventricular dilatation B3:IVH with ventricular dilatation Intraparenchymal lesions: 4 grades: W1:Subtle or diffuse echodensity W2: Definite, distinct echodensity W3: perventricular cystic formation (PVL) Intraparenchymal W4: echodensity of haemorrhagic type or other gross pathology W1 – W2: correspond to non-cystic PVL B1-3 plus W1-4 PDA: none, spontaneous/ pharmacologic closure, Surgical ligation RDS: presence or absence CLD: according to Bacalari criteria Infantile septicemia: verified by blood culture: staph epi, candida, naerobic bacteria, other. (The other predictors were not specifically defined)	1) Griffith's Developmental Scale for Psychomotor development 2) Total Score (sum of subclasses scores) 3) Individual subclasses Scores (Assessment at 10 months of age)	Griffith's developmental scale, standardized for Swedish infants: 5 subclasses Scale A: locomotor function, Scale B: Personal-social competence, Scale C: hearing and speech Scale D: Hand and eye coordination: fine motor grasping Scale E: Performance: Perception and intelligence scale Scale Specificity of subclasses: limited when infants tested are immature/ Specificity increases with age.

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Koller 1997 97193708	General: 1) Birth weight 2) GA 3) Illness severity -neonatal health index 4) maternal education CNS: Neurological status at 1 year	Neurological status at 1 year corrected age: (1) abnormal, a severe abnormality, such as CP, global hypotonicity, chronic seizure, hydrocephaly, blindness, or severe sensorineural hearing loss, for which a diagnosis could be established (2) suspicious, some atypical or questionable signs in tone, reflexes, gait, or movement, but for which there is no definitive diagnosis or syndrome (3) Normal, based on a completely normal neurologic examination	**CNS:** Neurodevelopmental: Cognitive delay	Bayley MDI, Stanford-Binet IQ, Wechsler scale
Murphy 1997 97192793	General: GA, Apgar score CNS: Intracranial/Intraventricular hemorrhage White Matter Disorder Periventricular leukomalacia Ventriculomegaly/Ventricular diration. Seizures Cardiovascular: Bronchopulmonary dysplasia Preurmothora GI: Total Patenteral Nutrition Other: Infectious disease, Transfusion PDA, Prolonged ventilation.	Definitions not given for most predictors.	**CNS:** Cerebral palsy	Obtained diagnosis from regional registry of childhood impairments.

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Schendel 1997 98033417	*General Predictors* 1) Birth Weight- 3 groups VLBM (very low birth wt) MLBW (moderately low birth wt.) NBW (normal birth wt) *Other Predictors* *1)* Other: married at birth *2)* Other: Medicaid recipient	ND	**CNS:** Other: Developmental Delay **Pulmonary Outcomes** Birth weight	Developmental delay measured by Denver Developmental Screening Test II. "DELAY" defined by 9 measures of performance on Denver Developmental Screening Test II at age 15 months corrected.
Thompson 1997 97268338	Other predictors: 1) Neurobiological Risk Score (NBRS) 2) Hasseles Scale Score (HSS) → divided mothers into high and low risk; a "stress" score 3) Maternal variables	NBRS→weighted scored of medical events: ventilation, acidosis, seizures, IVH, PVL, sepsis and hypoglycemia	**CNS**: Neurodevelopmental: Cognitive delay	McCarthy scales at age 4 years Definition: not clear on how well validated either of the predictors are. Definitions of NBRS and Hasseles scores are probably OK, but I am not familiar with these.
Victorian Infant Collaborative study Group 1997 98026322 ***There are a series of Victorian articles in LBW-ALL.** ***This study will be combined in LBW-ALL table**	General: BW Other: period of time when born	Each sample were subdivided into BW=500-749 g and BW=750-999 g 1985-1987 vs. 1991-1992	**CNS**: Cerebral palsy Neurodevelopmental: Cognitive and motor delay Disability **Ophthalmology**: Blindness **Audiology:** Deafness or hearing aid	CP was not defined Bayley Scales of Infant Development DQ, using the published mean and SD Disability: "Sever" – bilateral blindness, cerebral palsy with the child unlikely ever to walk, or a DQ score <-3SD; "Moderate" – bilateral sensorineural deafness requiring hearing aids, cerebral palsy in children not walking at 2 but expected to walk, or a DQ score from –3SD to <-2 SD; "Mild" – cerebral palsy but walking at 2 , or a DQ score form –2 SD to <-1 SD.

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Battin 1998 99002694	General: 1) GA (23-25 wks) In comparative component with Historical control group General: 1) Birth during a period with routine use of: antenatal steroids, surfactant and dexamethasone for BPD (vs birth in presurfactant, presteroid period)	ND	**CNS:** 1) Neurodevelopmental outcome 2) CP 3) Low MDI (below 2 SDs) **Ophthalmology- Audiology:** 1) Blind, Deaf	Neurologic exam Bayley scale: MDI, PDI Formal hearing test Ophthalmologic examination
Bos 1998 98218970	General predictors Quality of general movements CNS Head ultrasound finding of transient periventricular Echodensities	Diagnosed by US examination. The duration was determined for the frontal and the parieto-occipital region separately and classified according to four categories: (1) no echodensities, (2) echodensities between 1 and 6 d, (3) echodensities between 7 and 13 d, and (4) echodensities persisting for more than 14 d.	**CNS:** Neurodevelopmental CP Cognitive delay	Developmental trajectory of general movement quality, analyzed according to Prechtl's method. Movements were judged globally based on visual Gestalt perception. Normal general movements are characterized by complexity, variability, and fluency.
Cherkes-Julkowski 1998 98262696	General: GA Other: Mother perception of child competence	ND	**CNS:** Cognitive delay Neurodevelopmental School problem Neurological Impairment (NI) Attention Deficit Disorder (ADD) **Audiology:** Language	Cognitive delay, measured by Stanford-Binet School programs (school concerns = SC) Learning disabilities (LD) Neurological Impairment (NI) Attention deficit Disorder (ADD) Language impairment = LI – dx made by speech and language clinician

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Emsley 1998 98238139 (CNS+ All)	*General* 1) Birth weight 2) GA *CNS* 1) Other: significant cranial U/S findings (see page 1 for definition) *Other:* 1) Illness acuity – CRIB score 2) Other: male sex	CRIB score is determined by BW, GA< congenital malformations, max base excess in first 12 hours, minimum FIO_2 in first 12 hours and max FIO_2 in first 12 hours	**CNS :** CP Neurodevelopmental Disability : normal, mild, moderate severe Behavioral disorders Learning disabilities Seizure disorder Developmental Delay **Ophthalmology :** Blindness Other Squint **Audiology:** Deafness Speech delay	ND "Normal"- No clinically apparent developmental abnormality causing functional disability "Mild Disability" - myopia, language delay, mild hearing loss, hyperactivity or clumsiness. "Moderate Disability" – Spastic diplegia, hemiplegia, moderate learning disability (DQ 50-69) "Severe Disability" – spastic quadriplegia, blindness, deafness (> 70 dB), uncontrolled epilepsy or severe learning disability (DQ < 50) and multiple disabilities. Not defined or how it is measured ND DQ < 70 > 70 dB, dot defined or how it is measured ND
Pasman 1998 98196839	*CNS* 1) Other: Neurobiologic risk score (NBRS) 2) Neonatal Neurologic Inventory (NNI) table 1	13 items of NBRS 4 items of NNI	**CNS** Neurodevelopmental: Cognitive delay Mental retardation	Standardized testing: VMI Leiden diagnostic test WISC-R BWVR ADIT
Rogers 1998 98438124	Birth weight GA Periventricular Bronchopulmonary dysplasia Hospital/Health care resource utilization-length of stay	IVH according to discharge clinical record diagnosis	**CNS:** CP **Neurodevelopmental:** Growth failure	According to discharge clinical record diagnosis (quadriplegia, diplegia, or hemiplegia) Weight-for-age z score was more than 2 SD below the mean and subsequently fell below –2 SDS

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Spinillo 1998 98237382 Spinillo, 1997 98021316 & 97277958 ***have some overlapped sample with spinillo, 1994**	General predictors: 1) Birth weight' 2) GA 3) SGA/IUGR 4) Maternal disease (diabetes, respiratory, cardiovascular, renal etc) 5) Antenatal steroids Other predictors: 1) Infectious disease 2) Dexamethasone 3) Perinatal factors (Socioeconomic factors, pregnancy variables, Delivery variables) 4) Meconum-stained amniotic fluid	Preeclampsia defined as: 1) Diastolic BP> 90 2) Systolic BP> 140 3) Proteinurea> 0.3 g Severe preeclampsia defined as: 1) Diastolic BP> 110 2) Systolic BP> 160 3) Proteinurea> 3 g Intrapartum Fetal HR abnormalities: • Late decelerations 1) Variable decelerations 2) Bradycardia Tachycardia	**CNS** CP Neurodevelopmental: Mental retardation	CP: Spastic diplegia, hemiplegia, tetraplegia , With moderate to severe interference with function, With or without mental retardation (MDI< 71) Bayley scales
Tin 1998 99046171	General: GA (23-31 wks)	ND	**CNS:** Neurodevelopmental: 1) Mental retardation (IQ < 75) 2) Other; disability (severe, severe sensorimotor) 3) Other: development - assessed by Griffith's mental and developmental scales	Definition of "severe disability" and "severe sensorimotor disability" were not given in this article . They referred to the wrong reference for these definitions, therefore, I am unable to find the definitions. Reference population for Griffith's scales were "preterm babies in the study S serious sensorimotor disability"

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Burguet 1999 99126269	General Predictor: 1) Male gender Cardiovascular 1) Bronchopulmonary dysplasia Other predictor: 1) Infectious disease neonatal sepsis 2) Maternal hypertension 3) RDS 4) Outborn birth 5) Race 6) Urban residence 7) Family precariousness = father absent or both parents unemployed 8) PROM > 48 hours (preterm) 9) Monochorionic placentation 10) Singleton placentation 11) Dichorionic placentation	RDS diagnosed by chest radiography examination PROM = premature rupture of membrane	**CNS:** CP PVL	One or more of the following signs was observed – hemiplegia, diplegia, tetraplegia, dystonia, athetosis, blindness, or neurosensory deafness
Cooke 1999 99257637	General predictors: Antenatal steroids Period of birth CNS: IVH Periventricular leukomalacia Other: Surfactant use	ND	**CNS:** CP	Data from Regional Cerebral Palsy Register

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Cooke 1999 99380719	Birth weight CNS: white matter disorder, periventricular leukomalacia, ventriculomegaly, MRI abnormality, thinning of corpus callosum, povencephaly, Brain measurements (multiple)	ND	**CNS:** Motor delay Cerebral palsy Cognitive delay Mental retardation Behavioral disorders School problems Learning disabilities	IQ: WISC III Motor delay (motor disability): Movement of ABC scores Mental retardation Behavioral disorders School problems Learning disability: Suffolk Reading Scale. Basic Math and Spelling Test

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Finer 1999 99436635	*CNS Predictors:* Delivery room resuscitation (DR-CPR)	Defined as chest compressions and/or epinephrine used.	**CNS:** *Neurodevelopmental* 1) Motor delay 2) Post hemorrhagic hydrocephalus (PHH) 3) Apgar scores 4) IVH/echolucenies 5) Developmental 6) White matter injury	In the first year, neurodevelopmental assessment by Amiel-Tison Neurologic Screen. Thereafter, used Knoblick-Gesell Developmental Inventory. "Neuromotor Outcome - questionable": hypotonia, hypertonia, asymmetry "Neuromotor Outcome - abnormal": cerebral palsy "Developmental Outcome - normal": both mental and motor composite scores ?86 "Developmental Outcome - questionable": either score 76-85 "Developmental Outcome - abnormal": either score <75 "Neurodevelopmental Outcome - normal" if both neuromotor and developmental evaluations are normal. "Neurodevelopmental Outcome - questionable" if either neuromotor or developmental evaluations are questionable. "Neurodevelopmental Outcome - abnormal" if either neuromotor or developmental evaluations are abnormal. "White matter injury": presence of grade 4 hemorrhage, echolucencies, or ventricular dilation unrelated to hemorrhage.

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Futagi 1999 99450356	General: 1) Birth in surfactant era 1989-1993 vs Birth in pre-surfactant era 1981-1986	Not specified further	1) Normal neurodevelopmental outcome 2) Cerebral palsy 3) Mental retardation 4) Borderline intelligence (Assessment between 3-8 yrs, mean age of assessment was 6 yrs)	*1)* Normal neurodevelopmental outcome: Absence of motor disturbances and developmental quotient and/or intelligence quotient more than 84. 2) Cerebral palsy: diagnosis based on Bax criteria (Outcome data also given for one child with spinal palsy: no definition given) 3) Mental retardation: DQ or IQ scores less than70 4) Borderline intelligence: DQ or IQ scores between 70-84, DQ and /or IQ scores: (of latest exam)according to Kyoto child guidance clinic development scale for children for subjects up to 7 yrs of age, Or according to the revised Wechsler Intelligence scale adapted for Japanese children for cases more than 7 yrs of age. (the results of gross motor skills in the former test were excluded for cerebral palsy children when computing DQs)
Kim 1999 99416608	Other Predictor-Perinatal factors	ND	**CNS:** CP **Neurodevelopmental:** Development delay	Non-progressive, often changing motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of development Delay in parameters for motor development of more than two months according to the stages of motor development by Vojta

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Krageloh-Mann 1999 99431017	CNS: 1) Intracranial/ Intraventricular hemorrhage 2) PVL 3) Cerebral blood flow 4) Cerebral oxygen delivery	CBF measured with ^{133}Xe clearance at 12.9 hours of life (range 1-48hr) Cerebral oxygen flow calculated as CBF x ART 02 content	**CNS:** Spastic CP **Neurodevelopmental**: Motor delay Mental retardation Anatomical abnormalities on MRI **Ophthalmology:** Visual blindness	Stott-Moyes-Henderson test - Spasticity of extremities with flexor hypertonicity, increased tendon reflexes and characteristic posturing Motor disability was graded as severe if the child could not walk unaided at the age of 5 y, otherwise as mild WISC
Salokorpi 1999 99353226	General: BW, GA, SGA/IUGR, Maternal disease CNS: IVH grade III or IV PVL Other: duration of ventilation, hypotension, hypocarbia, infectious disease	ND	**CNS:** CP Mortality by 2 years	A diagnosis of CP was confirmed when abnormal muscular tone, persistent or exaggerated primitive reflexes and major delay in motor development were found. The classification of CP syndromes was based on the definition by Hagberg et al.
Shepherd 1999 99165413	Ophthalmology : VEP (visual evoked potential)	One flash per second 20 cm from eyes. Each trial included 30 responses. 2 trials averaged. In preterms, VEP measured at 3 day of life in groups < 34 weeks, 34-36 weeks and 40 weeks, when 3,6-12 months.	**CNS:** Cerebral palsy	No definition of CP given
Stathis 1999 99325758	CNS Predictors 1) Other: head circumference category 2) Head growth velocity	Self-explanatory	**CNS:** Neurodevelopmental: Cognitive delay Behavioral disorders-ADHD School problems Learning disabilities	Academic problems--Answer questionnaires given to teacher ADHD--Dr. Paul rating scale McCarthy's scales

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Vohr 1999 99332101	Intracranial/Intraventricular hemorrhage	Cranial ultrasound finding	**CNS**: CP Neurodevelopmental: Cognitive and Motor delay	CP diagnosed by routine neurological exam. CP was based on the presence of hypertonicity, hyperreflexia, and dystonic or spastic movement quality in the affected limbs. Stanford-Binet Intelligence Scale PPVT-R
Agustines 2000 20279724	General predictors: 1) BW (500-750) 2) GA	ND	**Neurodevelopmental outcome:** Bayley scale 1) MDI 2) PDI 3) Overall neurodevelopmental outcome 4) Neurodevelopmental outcome stratified by GA (assessment at 30 months corrected age)	1) Normal development: Performance within 1 SD 2) Mild delay: Performance below 1 SD 3) Severe delay: Performance below 2 SD

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Breslau 2000 20298367	General: 1) LBW (vs Normal BW= NBW) 2) Urban (vs suburban setting) 3) Maternal smoking during pregnancy	ND	**CNS/Behavior** 1) Behavioral problems in 3 domains: Attention , Externalization Internalization 2) Severe attention problems (above a cutoff point of 67) Assessment at 11 yrs of age (assessment at 6 yrs: reported in another publication)	Mother's rating was done with: Child Behavior Checklist (CBCL) Teacher's rating was done with Teacher Report Form (TRF) (teachers were blind to the BW information of the child) Assessments at 11 yrs were conducted blindly to the results of assessments at 6 yrs (reported in another publication) Attention problem subscale; 20 items Externalization problem subscale: 2 subclasses Internalization problem subscale: 3 subclasses
Buhrer 2000 20280896	CRIB score	Routinely measure on the first day of a baby's life. CRIB score determined from: BW, GA, congenital life-threatening malformations, worse base excess, min+max FIO2 in first 12 hrs of life	**CNS:** Neurodevelopmental	Griffith's test
Grether 2000 20448692	Received Magnesium sulfate	Chart review	**CNS:** CP	Mild, moderate, or severe CP assessed from record of 2 state agencies.
Katz-Salamon 2000 20332284	Cardiovascular or pulmonary predictors: chronic lung disease	1st week ? acute lung injury; clinical signs; supplemental O_2 at 28 days; typical CXR	**CNS:** Neurodevelopmental: Cognitive delay CP	Griffith's development scale Movement assessment index (MAI): the original number of items was reduced to include only those reported to be the most valid as predictors of CP

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Marlow 2000 20150342	**General:** 1) Birth weight 2) Apgar score 3) Illness severity (CRIB) scores **CNS:** 1) Maximum bilirubin level 2) Abnormal cerebral US scan **Audiology:** 1) Sensorineural hearing loss **Cardiovascular/Pulomonary:** 1) Duration of intubation, respiratory support, oxygen, pH<7.2, base excess 2) Dopamine 3) Furosemide 4) Indomethacin use **Other:** 5) Netilmicin 6) Vancomycin 7) Positive blood cultures 8) Bilirubin >200 ?mol/l 9) Bilirubin>GA x 10 10) Creatinine >60 mmol/l 11) Netilmicin 12) Vancomycin Combination of the above: 1) Bili.200 + acidosis 2) Bili> 200 + sepsis 3) Bili >200+ netilmicin 4) Bili> 200+ vancomycin 5) Bili>200+ furosemide 6) Peak bil+ acidosis 7) Peak bili+ sepsis 8) Peak bili+ netilmicin 9) Peak bili+ furosemide 10) Creatinine>60+ netilmicin or vancomycin or furosemide 11) Netilmicin+furosemide • Vancomycin+ furosemide	Not further specified	In case control component: **Audiology:** Sensorineural hearing loss (SNHL) of 50 dB within 9 months from birth In Longitudinal component: **CNS:** Cerebral palsy at 12 months of age in the 2 groups (SNHL and control group)	Cases of SNHL were identified if the hearing loss had been identified within 3 months of discharge home, (within 9 mo from birth); after excluding cases with conductive hearing loss, possible congenital cause, or had neonatal bacterial meningitis

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Palta 2000 20096107 (CNS+Eye)	General: 1) Birth weight 2)Antenatal steroids 3)Multiple birth CNS: Intracranial/ Intraventricular hemorrhage Ophthalmology: Retinopathy of Prematurity (ROP) Cardiovascular/ Pulmonary: 1)Surfactant administration 2)Respiratory score Other: 1)Multiple birth 2)Socioeconomics 3) Number days in NICU	BW ≤1500 gms VLBW -Baseline respiratory scores = disease 1st 3 days of life 0-100 based on increasing severity BPD: O2 use at 36 wks post conceptional age postnatal used corticosteroid use mechanical ventilation or both = severe BPD at 30 days	**CNS:** CP Neurodevelopmental: Functional assessments **Ophthalmology:** Visual impairment Blindness Standardized scores for **self care, mobility and social function**	CP: physician dx at parent interview and confirmed by clinic record abstraction as well as blindness and use of corrective lenses. Pediatric Evaluation of Disability Index (PEDI): standardized scores for self care, mobility and social function
Torrioli 2000 20275419 (CNS+Eye)	General: 1) Birth weight 2) GA 3) SGA/IUGR	ND	**CNS:** Neurodevelopmental: Motor delay Cognitive delay Behavioral disorder **Ophthalmology:** Visual impairment	For VMI &WISC measures, “abnormal” was defined as under the 5th%tile; “normal” was defined as over 15th %tile of a control group VMI Movement WISC Conner’s relent symptom questionnaire
Valkama 2000 20233239	**General predictors:** Birth weight GA SGA/IUGR **CNS predictors:** IVH White matter disorder Periventricular leukomalacia MRI findings	IVH grading according to Papile PVL grading according to DeVries	**CNS:** Cerebral palsy	Infants whose motor development was delayed and who had abnormal muscle tone and motor function as an impairment or disability at a corrected age of 18 mo were defined as having CP in the sense of Hasberg et al.

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Vohr 2000 20295211	*General:* 1) Birth weight 2) Maternal disease (HTN) 3) Antenatal steroids *CNS:* 1) Intracranial/Intraventricular hemorrhage (GR 3 to $ IVH/PVL) *Cardiovascular or Pulmonary:* 1) Chronic lung disease (oxygen requirement at 36 weeks) 2) Other: postnatal steroids 3) Other: Surfactant *Gastrointestinal:* 1) Necrotizing "enterocolitis" *Other:* 1) Other: male sex 2) Other: Race (white) 3) Other: sepsis (early and late onset) 4) Other: maternal education	GR 3 to 4 IVH. PVL undefined sepsis undefined	**CNS :** Cerebral palsy Neurodevelopmental: 1) Motor delay (sitting, walking, pincer grasp, feeding) 2) Seizure disorder 3) Post hemorrhagic Hydrocephalus (PHH) and shunt 4) Other: Neurologic exam (normal; abnormal) 5) Development (MDI and PDI by Bayley II Scale) **Ophthalmology :** 1) Visual impairment (any) 2) Blindness (unilateral, bilateral) **Audiology:** 1) Hearing disorders	"normal Neurologic exam": no abnormalities on neurologic exams
Dammann 2001 21334215	*General Predictors:* 1) Birth weight 2) SGA/IUGR *CNS Predictors:* 1) Intracranial/ Intraventricular hemorrhage *Other predictors:* 1) Infectious disease 2) Perinatal factors - PTL, PROM, C-section	ND	**CNS:** CP	ND

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Gaillard 2001 21221175	In retrospective case-control component: **General:** 1) shorter length of ventilation beyond 27 (but not 50) postnatal ds vs more prolonged ventilation beyond 49 ds 2) Number of days "off"" ventilator in the groups of 27-49 postnatal ds ventilation and the group of >49ds ventilation In retrospective cohort with historical control group component: **General:** 1) Birth in a period where Antenatal steroids and Surfactant were more routinely used vs birth in pre-surfactant pre-antenatal steroid period	Not further specified	**CNS:** Neurodevelopmental outcome: 1) Normal 2) Mild disability 3) Moderate disability 4) Severe disability	Normal neurodevelopmentally: no clinically apparent neurodevelopmental abnormality causing functional disability Mild disability: e.g. myopia, language delay, mild hearing loss, hyperactivity or motor clumsiness. Moderate disability: for example: spastic diplegia, hemiplegia or moderate learning disability (Developmental Quotient: 50-69) Severe disability: e.g. spastic quadriplegia, blindness, deafness (loss of 70 decibel or more), uncontrolled epilepsy, or severe learning disability (developmental quotient <50). Infants with multiple disabilities. (3 yrs CA)
Horwood 2001 20574647	Other: Breastfeeding duration	Retrospective questioning	**CNS:** Neurodevelopmental: Cognitive delay Mental retardation	WISC-R verbal and performance IQ scores at age seven years.

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Nadeau 2001 21163667	General: GA Other: Family adversity Index	Evaluated at 5 years 9 months, was developed using SES data such as the family status (two-parent, single-parent, blended), age of each parent, their respective levels of education, and professional occupations. 0=low ~ 7=high	**CNS:** Neurodevelopmental: Motor function Cognitive delay Behavioral disorders **Behavior**	Neuromotor development index: Huttenlocher neurological task test McCarthy Scales of Children's Abilities Behaviors were assessed by peers, teachers, and parents: RCP, TRF, parent's CBCL
Pierrat 2001 27221167	*CNS Predictors:* Periventricular leukomalacia (cystic) in ≤32 wk GA infants	Grade II - Transient periventricular densities, evolving into small cysts. Grade III - Transient periventricular densities, evolving into large cysts.	**CNS:** Neurodevelopmental: Motor delay Cerebral palsy	Motor delay - 12, 18, 24 month outcome as the protocol of Amiel-Tison and Stewart, and Touwen Criteria of Hagberg et al.

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Leonard 1990 90204169	Neurologic abnormalities: Oxygen group (no IVH and no parenting risk): 0-29 days 9%, = 50 days 0%, p=NS among oxygen groups, total 6% IVH (no parenting risk factor): none 6%, Gr 1-II 0%, Gr III-IV 21% Parenting risk (no IVH): absent 6%, Present 17%, p=NS Cognitive deficits: Oxygen (no IVH and no parenting risk): 0-29 days 18%, = 50days 7%, total 17% IVH (no parenting risk factor): none 17%, Gr I-II 29%, Gr III-IV 50%, p < .005 between none and Gr III-IV groups Parenting risk (no IVH): Absent 17%, Present 75%, p<.001 NO cognitive risk factors: Low socioeconomic status with no parenting risk 74% Low socioeconomic status with parenting risk: 20% p<.02 Abnormal cognitive outcome (logistic regression): Oxygen: NS IVH: Grades 0-IV p= .0042, Gr I-II p=.18, Grade III-IV p=.003 Parenting risk with no IVH p= .0002 Low socioeconomic status p= .0107	Almost 30% dropout rate. Incomplete description of study groups No description of how neurodevelopmental assessment was done (who evaluated and were they blinded to the group). Conclusion that antenatal steroids and surfactant improves neurologic outcome is inappropriate since he had no control group that did not receive these treatments.	No data on funding source
Lucas 1992 92122860	Fortified breast-milk-fed vs. Minimally supplemented breast-milk-fed: Gross motor development/Knobloch scale: (Not significant) 102.7 ±1.8 ; 102.9±2 Language development/Knobloch scale: (Not significant) 92.6±0.9 ; 92.1±1.1 Social development: (Not significant) 104.6±1.1 ; 105.6±4 Motor development/Bayley: (Not significant) 92.3±1.6 ; 89.9±1.5 Mental development/Bayley: (Not significant) 106±2 ; 105.8±2 Social development/Vineland (Not significant) 118.9±1.7; 115.8±1.7	Not exclusively breast fed: in both groups total maternal intake was < 50 % breast milk with the Differential loss to follow up not reported-cannot determine BWT/GA of groups at follow-up	No data on funding source

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Robertson 1994 94181384	**CP** 500 –749 g (20) 1/20 750 –999 g (54) 6/59 1000-1249 g (84) 4/84 500-1249 g (163) 11/163 (**6.7%)** **Vision loss** 500 –749 g (20) 2/20 750 –999 g (54) 0/59 1000-1249 g (84) 0/84 500-1249 g (163) 2/163 (**1.2%)** **Hearosensory** 500 –749 g (20) 1/20 750 –999 g (54) 0/59 1000-1249 g (84) 1/84 500-1249 g (163) 2/163 (**1.2%)** **Mental retardation** 500 –749 g (20) 3/20 750 –999 g (54) 0/59 1000-1249 g (84) 0/84 500-1249 g (163) 3/163 (**1.8%)** **Convulsive disorder** 500 –749 g (20) 0/20 750 –999 g (54) 0/59 1000-1249 g (84) 0/84 500-1249 g (163) 0/163 (**0%)**	Does not give detailed characteristics of cohort	Study was private funded
Spinillo 1994 94257064 ***have some overlapped sample with spinillo, 1997**	Studied outcome of LBW infants after 3rd trimester bleeding. Controls were LBW's without 3rd trimester bleeding. Abruption, n = 40; previa, n= 22; unclassified bleeding, n = 15; controls, n = 153. Group Grade 3-4 IVH Cystic PVL Major handicap Poor Outcome Abruption 12.5%* 5% 11.1%+ OR = 3.9 (1.2, 2.1) Previa 13.6% 0 0 OR = 0.9 (0.2, 3.6) Unclassified 6.7% 0 0 OR = 0.6 (0.1, 0.3) Control 3.9% 0.6% 0.7% Reference group *P = 0.02 vs. control +P = 0.007 vs. control	Not all severe VLBW No information regarding frequenting of VLBW Bayley test score information no presented	No data on funding source

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Chen 1995 96009403	All of the LBW preterm infants with normal brain US finding (N=12) had "normal development". Two (17%) of them developed spastic CP. All of the LBW preterm infants with abnormal brain US finding (N=5) showed signs of spastic CP.	No reference of DDST Cases report without statistical analyses Vague or no definition of outcomes	No data on funding source
Goetz 1995 96119489	Tone abnormalities : (PVL) 12/12 Seizure disorder: (PVL) 1/12 Strabismus: (PVL) 3/12 Cognitive delay: (PVL) 6/12 mild 2/12 severe 4/12 They found cognitive delay in 6 of 12, seizures in 1 of 12 and strabismus in 3 of 12	Missing information Small sample	No data on funding source

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Speechley 1995 96356544	**General Health outcome:** Among boys around 12 yrs of age: NICU graduates as opposed to normal boys: 1) Are living with more chronic health problems 2) Are more likely to have a physical impairment 3) And have been hospitalized more often. Among girls around 12 yrs of age: NICU graduates as compared to normal girls: No statistically significant differences in their physical health outcome. Among NICU graduates, boys were not different from girls in their long-term physical health outcomes. **Emotional and Social well being outcomes:** Among girls around 12 yrs of age: NICU graduates as opposed to normal girls: 1) Had significantly lower social competence 2) Lower social support 3) And Lower self-esteem. Among boys around 12 yrs of age: NICU graduates as compared to normal boys: 1) They had no difference in their emotional or social well being. There was no interaction between family's socioeconomic status and long term outcomes among NICU graduates. Analytically: The **physical health outcomes** at 12 yrs were (**Boys NICU** grads vs Boys NNN grads/ **Girls NICU** grads vs Girls NNN grads) • Chronic physical health (mother's report): 2.8 vs 1.8 (p<0.005)/ 2.4 vs 1.3 • Lifetime hospitalizations (mother's report): 2.5 vs 1.6 (p<0.005)/ 1.7 vs 0.4 • Physical impairments (mother's report): 0.29 vs 0.10 (p<0.005)/ 0.22 vs 0.06 • Perception of child's heath (child's report): 21.6 vs 22.2/ 21.1 vs 21.9 • Perception of child's health (mother's report): 16.9 vs 17.7/ 16.8vs 18.0 **Emotional and social well being at 12 yrs:** (Boys NICU grads vs Boys NNN grads, Girls NICU grads vs Girls NNN grads) • Internalizing problems (child's report):15.3 vs 15.5/ 18.2 vs 14.8 • Externalizing problems (child's report): 15.9 vs 16.0 / 14.3 vs 13.5 • Social competence (child's report): 109.1 vs 113.9 / 101.7 vs 115.7 (p<0.005 • Social support (child's report): 81.6 vs 83.2/ 79.9 vs 86.1 (p<0.005) • Self esteem (child's report): 31.9 vs 32.4/ 29.8 vs 32.5 (p<0.005) • School performance (mother's report): 4.5 vs 4.6/ 4.8 vs 5.3	1) There is an Inconsistency in Mother's appreciation of their child's physical health: mothers of NICU graduate boys reported that their children had more physical impairments than NNN boy graduates; however, their overall perception of their child's health status was not any different from NNN boys graduates. 2) Some of the outcomes 3) Collected are prone to recollection bias (e.g., frequency of lifetime hospitalizations).	1) In this NICU cohort, only 36% of infants had BW<2500 g and only 5% had BW < 1500 gs, reflecting more NICU populations in the 70s and early 80s, than the current ones. 2) It is unclear whether statistically significant differences in psychometric scales reflect clinically significant differences in the emotional and social wellbeing of these children. 3) Given the fact of many negative findings, post hoc power analyses demonstrated that the study had an 80% power to detect a 40% difference between the 2 groups. 4) The fact that girls ex NICU graduates had a more substantial psychological effect than boys may reflect that girls are further into adolescence than the boys, experiencing the sequelae earlier. Thus in order to determine whether the differences observed are a temporary effect/related to adolescence, this cohort had to be followed further into their teenage years

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Wildin 1995 95385294 Wildin 1997 97422739	High risk (HR) preterms, low risk (LR) preterms and full term controls. Most infants who were classified as high risk were classified as such due to BPD. Bayley MDI and PDI at 12 months corrected age: Group n Bayley MDI Bayley PDI HR 49 92.8 (24.9) 89.8 (20.7) LR 92 103.8 (16.3) 99.1 (19.5) *Control 114 108.2 (11.3) 108.5 (12.3)*	Preterm HR (high risk) Group: 84% were HR because of BPD only, so this groups is really a BPD group Many exclusion criteria Full developmental evaluation only done on a subgroup; others only partly examined	No data on funding source
***Data from same longitudinal study as Anderson, 1996 96314587 & Smith, 1996 97081985; overlapped sample**	**In Hierarchical linear models analyses:** Cognitive/Bayley, Stanford-Binet Medical risk category LR (N=115) Hierarchical linear HR (N=69) model P=0.02 Rate of mental development/Bayley, Stanford-Binet Medical risk category LR (N=115) HR (N=69) P=0.0004 Socioeconomic status and cognitive/ Bayley Stanford-Binet association not significant. Medical risk category SES and rate of mental development/Bayley, Stanford-Binet association not significant. SES and rate of mental development/Bayley, Stanford-Binet association not significant. Motor development not significant	Only analyzed infants retained through all 40 months Do not account for infants lost to follow-up Do not describe how group at 40 months differed in composition from group at enrollment. Use one-tailed test to achieve significance.	

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Anderson 1996 96314587 Smith 1996 97081985 (CNS+All) ***Data from same longitudinal study (U. of Texas Health Sciences Center in Houston and the U. of Texas Medical Branch in Galveston) as Wildin, 1995 & 1997; overlapped sample**	Cognitive Development (Bayley MDI) at 6 and 12 months, respectively: VLBW high risk (N=58): 100.7 (24.9), 92.8 (19.2) VLBW low risk (N=96): 106.8 (19.5), 103.8 (16.3) FT (N=119): 113.6 (15.8), 108.2 (11.3) Motor Development (Bayley PDI) at 6 and 12 months, respectively: VLBW high risk (N=58): 100.7 (24.9), 92.8 (19.2) VLBW low risk (N=96): 106.8 (19.5), 103.8 (16.3) FT (N=119): 113.6 (15.8), 108.2 (11.3) All groups differed significantly on MDI and PDI at 6 months ($p<.001$). At 12 months, only the high-risk infants differed from the term infants ($p<.001$). The means for all three groups at 6 and 12 months were within the normal range. However, significantly more high-risk infants fell within the moderately and severely delayed ranged than low-risk and term infants did (data not given) Total neurologic score at 6 and 12 months, respectively: VLBW high risk (N=58): 0.30 (0.23), 0.16 (0.22) VLBW low risk (N=96): 0.16 (0.17), 0.08 (0.12) FT (N=119): 0.05 (0.07), 0.04 (0.05) All groups differed significantly on total neurologic score at both 6 and 12 months ($p<.001$). Total score significantly improved from 6 to 12 months of age in all groups ($p<.001$). Total score in high-risk group still remained abnormal after improvement, while the score in low-risk and term infants were normal at 12 months of age. Assessed risk status in relation to outcome in areas of development of cognitive skills, communication development and daily living skills. Mental Age and daily living skills data are in months and language data are in raw scores:	Some comparison scores not shown The overwhelming majority of HR VLBW's were HR because of BPD with or without IVH Low socioeconomic status, inner city population	Study was government funded Significantly more abnormal neurologic scores at 12 month of age in VLBW high-risk infants compared to FT controls. Higher abnormal scores suggest degree of abnormality at 12 months depending on level of risk as neonate.

				Language	
Infant status	n	Mental Age	Daily living skills	Expressive	Receptive
High risk	88	11.6 (2.4)*	11.9 (2.65)	18.0 (5.4)#	14.2 (2.6)
Low risk	123	12.8 (1.7)*	12.97 (2.45)	20.5 (5.9)	15.3 (3.3)
Full term	128	12.9 (1.1)*	13.29 (2.0)	20.6 (4.7)#	15.3 (2.4)

*$p < 0.01$ for High risk v. low risk and full term
# $p < 0.01$ for high risk v. full term
Other differences are not significant.

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Author, Year	Associations found	Potential Biases	Comments
Kato 1996 97182916	Independent predictors of CP/MR Fetal malpresentation vs. cephalic presentation (p<0.01) Use of tocolytics vs. no tocolytics (p<0.005) Umb cord artery pH<7.2 (p<0.05) Major handicap (CP/MR/Blindess) increased in VLBW infants delivered by breech/vag (25%) v. ceph/vag (0%) vs. Breech/c-section (5%) vs. cephalic/c-section (8.5%) (p<0.05)	Retrospective –completeness data (predictors/outcomes) not known. Predictors and outcomes poorly defined. No FT comparison.	No data on funding source
Katz 1996 97145056	**Attention deficit** is measured by the CPT test (error of omission). **Hyperactivity** and impulsivity is measured by the CPT test (error of commission). There were no differences among the preterm infants with mild, moderate and severe intracranial lesions. However, there was a significant increase in both errors of commission and omission in preterm with mild lesions compared to full term infants as well as in preterm with severe lesions compared to full term infants. With increasing severity of lesions in preterm infants, increasing percentage in each group commit errors of commission. Even in the absence of detectable intracranial lesions, preterm infants are still at higher risk for developing attention deficits than full term infants.	Exactly how FT controls were selected in an unbiased way is not described.	No data on funding source This study does not explore relationship of attention deficits identified with the CPT test with actual school performance and achievement in this group of preterm infants. This study includes older preterm 26-34 weeks and does not include the extremely preterm 24-25 wk infants.

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Author, Year	Associations found	Potential Biases	Comments
Korkman 1996 96374730 Psy1996	Overall: the VLBW/SGA group had the poorest test results. The VLBW/AGA group was somewhat less impaired, whereas the birth asphyxia group performed at the control group level Impairment when present tended to be diffuse in all groups, affecting: psychometric intelligence, naming, visuo-motor performance, tactile finger discrimination, attention and phonological analysis. Predictors evaluation for **CNS outcome** (**Intelligence evaluation**): 1) VLBW/AGA was associated with poorer WISC-R score, when compared to healthy full term (FT) ($p<0.05$) 2) VLBW/SGA was associated with poorer WISC-R score, when compared to healthy FT ($p<0.05$) 3) VLBW/SGA was associated with poorer WISC-R score when compared to asphyxiated term infants (There was no difference in the scores between asphyxiated terms and healthy terms) Predictors evaluation for **CNS outcome** (**Neuropsychological evaluation):** 1) VLBW/SGA was associated with poorer NEPSY score ($p<0.05$) when compared to healthy FT 2) In the VLBW cohort, impairment when present tended to be diffuse (in all items examined). 3) VLBW/SGA was associated with poorer NEPSY score when compared to asphyxiated terms. Overall In the VLBW group (AGA and SGA) (n=77): 1) Apgar scores were not correlated with outcome measures 2) Arteria PH was correlated with FSIQ score 3) Intrauterine growth retardation correlated with NEPSY score 4) BW correlated with NEPSY score 5) There was no correlation between RDS, IVH , duration ofventilatory tx and cognitive dysfunction **Combined CNS / Ophthalmology outcome:** 1) VLBW/AGA: 21% (both mild and severe) 2) VLBW/SGA : 6/34 (18%) (mostly lids) 3) Birth asphyxia/ Term: 7/32 (22%) (mostly severe)	1) Cannot exclude potential selection bias (no description of patient flow in each group) 2) Cannot exclude diagnosis bias/no information on blinding of personnel evaluating developmental outcome component on PMHx. 3) The authors investigated associations between 7 predictors and many outcomes (the different subcomponents of WISC-R test and the NEPSY test)/ thus cannot exclude "multiple comparison" effect	Supported by non-governmental foundations

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Author, Year	Associations found	Potential Biases	Comments
Lucas 1996 96302121	Predictor evaluation for **CNS outcomes**: (Unadjusted analysis) Mother's choice to breast feed was associated with higher IQ scores at 7 years: (No mother's milk group vs Mother's milk group) • WISC-R verbal scale (mean): 92.0 vs 102.1 (p<0.001) • WISC-R Performance scale : 93.2 vs 103.3 (p<0.001) • Overall IQ: 92.8 vs 103.0 (p<0.001) (Adjusted regression analysis for confounders) Mothers choice to Breast feed infant: N=210 babies • Higher Verbal scale scores: (p<0.001) • Higher Performance scale scores (p< 0.0001) • Higher Overall IQ: (p<0.0001) Successfully breast fed infants only: (Received breast milk) N=193 babies • Higher Verbal scale scores: (p<0.0001) • Higher Performance scale scores (<0.0001) • Higher Overall IQ: (p<0.0001) Overall (Regression analysis) • Whether Received breast milk: offered advantage of 8.3 points (p<0.001) • Social class: -3.5/class (p<0.004) • Mother's education: 2.0/ group (p=0.01) • Female sex (p=0.01) • Days of ventilation: -2.6/ week (p=0.02)	Cannot exclude false association due to unrecognized confounders between the 2 groups as this study was non-randomized (despite matching for BW, GA, need for ventilation, NICU stay and other diets ; there are still exist important unconsidered confounders)	

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Author, Year	Associations found	Potential Biases	Comments
Rieck 1996 Psy 1996 06905005	In Prospective longitudinal component of the study: Predictor evaluation for **CNS** outcome: 1) Female Sex, HC percentile and Maternal education were independently associated with CGI score (r^2= 0.41, p< 0.001) 2) Age at assessment, GA and HC percentile were independently associated with Verbal scale score. (r^2= 0.36, p< 0.001) 3) HC percentile was independently associated with Perception-performance score (r2= 0.12, p< 0.05) 4) Neurologic complication and HC percentile were independently associated with Quantitative scale score (r2= 0.30, p< 0.01) 5) Neurologic complications and HC percentile were independently associated with Memory scale score (r2= 0.36, p< 0.05) 6) HC's percentile were associated with higher scores in the 4 scales of McCarthy's test and in the GCI . (p<0.05) In Cross sectional component of the study: Predictor evaluation for **CNS** outcome: 1) VLBW children with normal IQ, score significantly lower than the Middle class group on many cognitive tasks, and may demonstrate more learning disabilities than Middle class children 2) VLBW and Low Class children had significantly lower score in all scales of McCarthy's test , as compared to Middle Class children. (p<0.01) 3) VLBW had no different scores from Low class children. 4) Evaluation of the change of scores with age revealed that from age 3-7 yrs, VLBW advanced significantly less than Middle class children in Word Knowledge, Conceptual grouping and Numerical Memory backwards. 5) The gap between the scores of the 2 groups increased with age.	1) There was no matching, except for the age between VLBW and MC, LC children. Thus, there was no control for possible confounders, 2) Selection bias might exists: As only those that had completed the test were analyzed. (Only 58% of VLBW children had completed the test) 3) Selection bias also might exist as no information is given in the selection process of the 103 VLBW infants that had participated in the original study	1) No data on the absolute size of the association between predictors and outcomes were given. 2) Statistically significant correlation does not always mean a clinically significant association.

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Author, Year	Associations found	Potential Biases	Comments
Whitaker 1996 97040639	MR higher in LBW<2kg (5%) than in general pop distribution (2.5%) OR for MR vs Normal Intelligence: PVL/VE OR 65.83 (19.1-227.4) Isolated GMH/IVH OR 4.64(1.2-18.6) Verbal reasoning (Stanford-Binet area score) p<0.05 PVL/VE: 98.9 (10.8) GMH/IVH 102.9 (10.5) No abnormality 104.3 (10.9) Visual perception organization All abstract visual reasoning, visual-motor integration, and visual-perceptual stills were significantly (p<0.01 or p<0.005) were significantly lower for children who had PVL/VE compared to those with isolated GMH/IVH or No abnormality. 50% of MR attributable to PVL/VE independent of other factors.	(None)	Study was government and privately funded

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Author, Year	Associations found	Potential Biases	Comments
Blitz 1997 97154301	Developmental outcome: The mean MDI, PID, CLAMS Total, Expressive, and Receptive scores were 99.7 (19.8), 88.9 (19.8), 94.9 (23.0), 90.8 (26.2), and 99.7 (21.3), respectively. MDI < 70 9% PDI < 70 18% Language delay (>1 SD below the mean) 34% Significant language delay (>2 SD below the mean)12% Multiple regression analysis showed BW and surfactant did not relate to developmental outcome. BPD, PVL and IVH significantly increased the risk of impairment. PVL, BPD, seizures and hydrocephalus account for 29.7% of the variance on the MDI scores (F=10.05, p<. 001). PVL, IVH, and BPD accounted for 23 % of the variance on the PDI scores (F=9.6, p < .001). For the total CLAMS score, 11% of the variance was accounted for by PVL and BPD (F= 7.1, p < .002) Neurologic outcome: Multiple regression analysis showed low BW was not associated with neurological impairment. On the contrary, BPD and PVL significantly increased the risk (14.8% if variance; F=8.4, p<. 001). No other individual variables reach the significance level. CP: present 24 %, suspect 27%, No CP 49% Audiology: Hearing loss 16%. None of the children were profoundly hearing-impaired. Visual problem 18%. None were clinically blind	36% declined or did not appear (possible selection bias). Language assessment at 2 years is too early to determine more subtle language delays. No control group.	No data on funding source
Cheung 1997 97310950	Of the 21 preterms with IVH treated with rescue HFO, 8 (38%) has neurodevelopmental disabilities. Of the 8 preterms with grade III or IV IVH treated with rescue HFO, 6 (75%) has neurodevelopmental disabilities.	The title is “High Frequency Oscillatory Ventilation” but the authors state that a high frequency flow interrupt ventilator is used in their nursery. These distinct modes of ventilation should not be confused 60% mortality among cohort meeting inclusion criteria Time of follow-up not well standardized	No data on funding source

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Author, Year	Associations found	Potential Biases	Comments
Ekert 1997 97251211	Association between outcome (CP and/or developmental delay) and perinatal/neonatal variables: Multiple logistic regression analysis showed that only PVL was associated with abnormal outcome (PLV: p=0.0001)	(None)	Study was government funded

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Author, Year	Associations found	Potential Biases	Comments
Gerner 1997 97329414	Predictors evaluation for **CNS outcome:** 1) Healthy preterms did not differ significantly in psychodevelopmental outcome 2) Prematurity was not associated with the sum score in the Griffith's test 3) Prematurity was associated only with lower score Hand-Eye coordination scale 4) The predictors associated with poor psychodevelopmental outcome in preterms were (univariate analysis): General predictors: Low GA: Pearson correlation coefficient r= 0.19 (171 pts) (p< 0.05); Low BW: Pearson correlation coefficient r= 0.25 (171 pts) (p< 0.001); Intraventricular hemorrhage (IVH) + ventricular dilatation: Pearson correlation coefficient r= -0.27 (p< 0.001) CNS predictors: Periventricular Cystic leukomalacia, (PVL) r= -0.24 (p< 0.01); B1-3 + W1-4 U/S findings, r= -0.27 (p< 0.001) Cardiovascular predictors: PDA (n=72 pts), r= -0.32 (p< 0.001) Pulmonary predictors: Prolonged ventilatory therapy (n-94 pts), r= -0.39 (p< 0.001); CLD: (n=56 pts), r= -0.26 (p< 0.001) 5) Although the screening indicated that several risk factors were associated with adverse neurodevelopmental outcome- in the multiple regression model the contribution of individual variables was very low (less than 20%). 80% of the outcome variance still remained unexplained. 6) Only predictors independently associated with total sum score in Griffith's test were (multivariate analysis): combination contributed to outcome variance by 21%: Pulmonary predictors: Duration of ventilatory tx (r^2=16%) and CNS: PVL (r^2=5%) 7) Predictors independently associated with scores of individual subscales: Locomotor subscale : combination contributed to outcome variance by 14% • Duration of ventilatory tx (r^2=9%), PVL (r^2=5%) Personal-Social subscale: combination contributed to outcome variance by 17% • BW (r^2=10%), PVL (r^2=7%) Hearing and speech subscale: • Duration of ventilatory tx (r^2=13%) Hand and eye coordination subscale: combination contributed to outcome variance by 15% • PDA requiring surgical ligation (r2=11%), • Hemorrhage plus White matter lesions (r^2=4%) Performance subscale: combination contributed to outcome variance by 18% • Duration of Ventilatory tx (r^2=12%) and White matter lesions (r^2=6%)	1) In the comparative components (Group A vs C and Group B vs A), there was no control for possible confounders, as not appropriate matching was done between these compared groups 2) Cannot exclude diagnosis bias as no information is given about blinding of personnel performing the neurodevelopmental assessment on the infants' risk factors 3) Two many predictors investigated (28) for the total number of patients in the VLBW group (cannot exclude false associations found in the regression analysis) 4) Cannot exclude false associations due to chance, as multiple subgroup analyses were done (subclasses of Griffith's test) 5) The subclasses of Griffith's test have limited specificity, thus limited differentiating capacity at 10 months of age and especially for infants with neonatal complications as performance in one scale requires skills assessed in another scale.	Supported by non-governmental Foundations.

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Author, Year	Associations found	Potential Biases	Comments
Koller 1997 97193708	***Cognitive Development:*** Birth weight: P <0.001 Gestational age: P<0.001 Neonatal health index: P<0.01 Neurological status @ 1 yr: P <0.001 Male gender: P <0.005 Maternal education: P<0.005	Selection bias-does not include all VLBW infants- only those for whom all follow-up data are available--how are these different from the ones who did not show for follow-up?	Study was government funded
Murphy 1997 97192793	Apgar score <3 at 5minutes - 5.3% cerebral palsy Patent ductus arteriousus - 2.0% cerebral palsy Hypotension - 2.2% cerebral palsy Transfusion - 3.2% cerebral palsy Prolonged ventilation - 2.7% cerebral palsy Pneumothorax - 3.4% cerebral palsy Sepsis - 2.8 % cerebral palsy Total parenteral nutrition – 3.0% cerebral palsy Hyponatremia - 6.8% cerebral palsy Chorioamnionitis and neonatal sepsis - 7.1% cerebral palsy Any maternal infection and neonatal sepsis - 4.2% cerebral palsy Seizure - 10.0% cerebral palsy Parenchymal damage - 32.0% cerebral palsy	Ascertainment of CP was from registry--not examined as part of study Absence of CP was not obtained by exam as part of study Multiply definitions of predictor variables not reported Retrospective acquirement of risk factors-no standard definitions	Study was privately funded
Schendel 1997 98033417	Even apparently well VLBW with no overt physical impairment are consistently at higher risk for all measures of DELAY than MLBW or NBW infants. VLBW have DELAY in all areas of function with greatest risk for delay in gross motor domain. **"Abnormal"** – VLBW 10.9%, NBW 2.9%, p = 0.001 Personal-Social =1 delays: VLBW 7.1%, NBW 2.2%, p = 0.001 **Language = 1delays**: VLBW 8.8%, NBW 4%, p = 0.01 **Fine motor-adaptive = 1 delays**: VLBW 7.9%, NBW 2.2%, p = 0.001 **Gross motor =1 delays**: VLBW 10.7%, NBW 1.8%, p = 0.001	The people administering the Denver test were not blinded and were aware of degree of prematurity and this is a major source of bias. The adjusted age at f/u had very wide range 9-34 months	Study was government funded

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Author, Year	Associations found	Potential Biases	Comments
Thompson 1997 97268338	Neurobiologic risk score (NBRS) investigated to determine predictive value for performance on McCarthy Scales at 4 years age. N = 55. McCarthy Scale — Mean (SD) — Range General cognitive index — 89 (20) — 49-126 Verbal — 44 (10) — 21-65 Perceptual-Performance — 44 (12) — 21-69 Quantitative — 46 (12) — 22-67 Memory — 46(10) — 21-67 Motor — 42 (12) — 20-70 Also: The NBRS was not found to be predictive of the McCarthy General Cognitive Index; in multiple regression analysis only birth weight, gestational age and gender were significantly related to the McCarthy scores.	One institution No control group Combined high NBRS and intermediate NRS patients into one group	Study was government funded
Victorian Infant Collaborative study Group 1997 98026322 ***There are a series of Victorian articles in LBW-ALL.** ***This study will be combined in LBW-ALL table**	Birth weight < 1000g; assessed at 2 years corrected age. Cohort — n — DQ < -3 SD — DQ –3 to –2 SD — DQ –2 to –1 SD — DQ> -1 SD '91-'92 — 237 — 5.9% — 6.3% — 13.9% — 73.4% '85-'87 — 211 — 6.2% — 4.3% — 14.2% — 75.4% Cohort — n — Mild CP — Mod. CP — Severe CP — Any CP — Blindness — Deaf '91-'92 — 237 — 3.8% — 1.7% — 3.8% — 9.3% — 2.1% — 0.8% '85-'87 — 211 — NS — NS — NS — 6.6% — 4.3% — 0.5% Cohort — No disability — Mild Disability — Moderate disability — Severe disability '91-92 n = 237 — 71.3% — 14.8% — 7.2% — 6.8% '85-'87 n = 211 — 71.6% — 15.6% — 6.2% — 6.6%	Incomplete reporting of demographic data, methods and results.	Study was government funded

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Author, Year	Associations found	Potential Biases	Comments
Battin 1998 99002694	**CNS outcomes:** Major impairment was present in 36% of infants born at 23-25 wks GA, during 1991-1993 (N=44) 1) Cerebral palsy 9/44 (20%) 2) Low MDI 8/44 (18%) **Ophthalmology** outcome: 1) Blind 4/44 (9%) **Audiology** outcome: 1) Deaf 4/44 (9%) **Combined** outcome: 1) Overall impaired 16/44 (36%) 2) Multiple handicaps 6/16 (38%) Analysis of only 24-25 wks GA infants (N=43): Major handicaps: 15/44 (34%) The percentage of infants with major impairments and/ or multiple handicaps, for the 23-25 wks GA group, was the same in 1991-1993 and 1983-1989 periods (However, no data on the number of infants from this cohort that were actually followed up at 18 mo of age)	1) During 1991-93 period there is no concurrent control group for the comparative assessment of neurodevelopmental outcome 2) Group of infants of 23-25 wks GA, born during 1991-1993, was not matched to the historical control group born during 1983-1989. Possibility of confounders cannot be excluded. 3) No data were given on the number of infants in the historical control group that had f/up at 18 mo of age.	No report on source of funding
Bos 1998 98218970	The developmental course of the quality of general movements significantly correlated only with the duration of parieto-occipital echodensities (r=0.482, p<.02), while the duration of PVE frontal was not associated with the developmental outcome (r=0.241, NS)	No power estimates for defecting modest effects	No data on funding source
Cherkes-Julkowski 1998 98262696	No disorder identified: PT 25%, FT 75 % Attention deficit disorder: PT 17.8%, FT 7.1% Learning disability: PT 17.8%, FT 14.2% Language impairment: PT 3.5%, FT 0% Neurological impairment: PT 7.1%, FT 0% School concerns: PT 28.5%, FT 21.4% This group of only mildly preterm, seemingly healthy PT infants have significantly more disability than expected $\chi 2(5)=62.577$, p= .0001	Evaluators were people in the community and social system so that there may be significant variations in evaluations. Sample size too small for statistical analysis.	No data on funding source This study is more a study of predictability of the attention deployment test in identifying minimal brain dysfunction at 13 and 15 mos, rather than a study of predictors of long-term outcome.

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Author, Year	Associations found	Potential Biases	Comments
Emsley 1998 98238139 (CNS+ All)	**Disability in 1st cohort 1984-1989 of 23-25 wks**: Any disability: 38% CP: 21% **Data on 2nd cohort 1990-1994 of 23-25 wks:** CP: 18% Blindness due to ROP: 18%, Myopia: 15%, Squint: 13% Developmental delay (DQ < 70): 15% Deafness: 3 % Epileptic seizures: 0 Speech delay: 15% Clumsy, learning difficulties, behavioral disorder: 3% Disability: Mild 38%, Moderate 13%, Severe 18% **Infants with disability have lower GA, worse CRIB** scores and significant cranial ultrasound findings. In comparing the 2 cohorts, increased survival is associated with increased disability but mostly mild disability. No significant change in %CP. High CRIB score assoc. with disability.	Sample numbers small. Does not state when the assessments were carried out and whether the evaluators were blinded to the GA and history of the infants.	No data on funding source

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Author, Year	Associations found	Potential Biases	Comments
Pasman 1998 98196839	Assessment at 5 to 7 years of age. Full-term (FT) controls, neurologically normal low risk preterm (normal LR) infants, neurologically abnormal low risk preterm infants (abnormal LR), and high-risk preterm infants (HR). Risk classification was based on the neonatal neurologic inventory. Group / n / Total IQ / Verbal IQ / Performance IQ FT: 18 114 (17) 113 (18) 111 (14) Normal LR w/ GA 25-30 weeks: 15 108 (15) 107 (16) 106 (11) Normal LR w/ GA 31-34 weeks : 21 113 (15) 114 (18) 107 (10) Abnormal LR w/GA 25-34 weeks: 8 99 (12) 104 (12) 93 (14) HR w/ GA 25-34 weeks: 9 78 (20) 79 (19) 81 (19) HR infants excluded from statistical analysis. Term infants vs. all low risk infants: Total IQ, no significant difference. Verbal IQ, no significant difference. Performance IQ P = 0.02.	Year of birth not given Small numbers in subgroups (e.g., 8,9) Incomplete reporting of results	Study was privately funded
Rogers 1998 98438124	There are no association between GA, BW, BPD Length of stay with growth failure P>0.05 Growth failure with CPVL 16/41 CP with CPVL 39/41	(None)	Study was privately funded

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Author, Year	Associations found	Potential Biases	Comments
Spinillo 1998 98237382 Spinillo, 1997 98021316 & 97277958 *have some overlapped sample with spinillo, 1994	**CP prevalence** 12.3% in 24-33 wk preemies **Minor neurologic problems (abnormal tone or reflex but functionally normal) or borderline (71-84) Bayley MDI** : 16.1% **Factors assoc with increased CP:** PROM > 48 hrs OR 2.98 (1.12-7.96 CI 95th) Meconium-stained amniotic fluid OR 4.36 (1.69-11.2) Male sex OR 3.01 (1.32-6.71) Decreasing gestation: CP 22.2% in 24-25 wks, 23.1% in 26-27 wks, 14.5% in 28-29 %, 8.3% in 30-31 wks, 9.3% in 32-33 wk infants. CP Meconium-stained fluid (N=17) 41% (7/17%) Clear fluid (N=246) 13.4% (33/246) P=0.06 **CNS outcome:** 1) The incidence of cerebral palsy in this cohort of preterm infants was : 40/345: (12%), but this refer only to those survived: 391/450 (87%) and to those that completed the 2 yr f/up: 345/450 (77%) Predictors evaluation for **Survival at 2 yrs:** 1) Survival at 2 yrs was associated with higher GA (p<0.0001), higher BW, (p<0.0001) And History of fewer previous abortions. Predictors evaluation of **CNS outcomes**: (In a univariate analysis) From the maternal and neonatal characteristics and the pregnancy complication/predictors, those found to be associated with CP were Odds Ratio (95% CI) 1) Higher Maternal age 1.07 (1.0-1.15) 2) Lower GA 0.87 (0.76-0.99) 3) Lower BW 0.94 (0.87-1.00) 4) male gender 2.65 (1.28-5.50) 5) More Previous voluntary abortion (25% vs 7%) 4.51 (1.94-10.5) 6) Preeclampsia (5% vs 19%) 0.22 (0.05-0.94) In a multivariate regression model (including maternal age, BW Standard deviation score, GA and preeclampsia) only preeclampsia was independently associated with the risk of cerebral palsy: OR: 0.16 (0.04-0.74) The authors conclude a protective effect of preeclampsia against CP, in the absence of Mg sulfate utilization	1) Major confounding postnatal factors such as BPD, IVH, and PVL, which may be associated with CP, were not controlled for. 2) We cannot exclude selection bias. The associations found were relevant to the group of surviving infants with cerebral palsy who also had f/up at 2 yrs. A large number of infants were excluded from the analysis: 46 infants that were lost to f/up and 59 that had died.	No data on funding source

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Author, Year	Associations found	Potential Biases	Comments
Tin 1998 99046171	**Result of 1983 cohort at 6 years:** *Severe disability:* Sample 1: 4.4%, Sample 2 : 2.1%, Sample 3: 50% *IQ < 75 without sensorimotor disability:* Sample 1 : 4.9%, Sample 2 : 0, Sample 3 : 25% *Severe sensorimotor disability:* Sample 1 : 5.9%, Sample 2 : 21.4%, Sample 3 : 41.7% *Severe sensorimotor or cognitive disability:* Sample 1 : 8.4% (5 - 13.1%, 95% CI) Sample 2 : 21.4% (4.7-50.8%) Sample 3: 41.7% (15.2-72.3%) **Result of 1990 cohort at 2 years:** *Severe disability:* Sample 1: 7.9%, Sample 2: 15.4%, Sample 3: 57.1% **High f/u rate is critical because it may underestimate incidence of the outcome.**	No definitions of outcome, incomplete methods description, wrong reference	Study was privately funded
Burguet 1999 99126269	In univariate analysis: The prevalence of CP in LBW preemies with RDS (N=66) was 20%, compared to 9% in preemies without RDS (N=101). The difference was significant (p=0.04) Incidence of CP 7% in no PROM, 20% in PROM < 48 hrs, 30% in PROM 48h to 7 days, 11% in PROM >7 days, χ^2 trend: p= .004 In multivariate analysis: Controlling for environmental and maternal factors, the risk of CP was about 3 times in preemies with RDS, than preemies without RDS (adjusted OR 2.8, 95% CI 1.1-7.1). "The introduction of surfactant in the second stage of our study was not shown to have any impact on the incidence of CP among the children of this cohort." PROM = 48 hours (OR 4.3, 95% CI 1.6-11.8), p= .005 Monochorionic twin placentation (OR 6.0, 1.7-21.3), p = .007 RDS (OR 2.8, 1.1-7.1) PROM +, PTL + (OR 7.5, 2.2-26.2), p= .001	8% BW>2000g Nonstandard definition of CP Suspected infant (mild hypotonia or delay to normal acquisition) were included in the normal group Evaluations done by community physician of parents' choice so, no standardization, and unblinded Used uncorrected age	No data on funding source Severe disability is common among extremely preterm infants of GA 22-25 wk

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Author, Year	Associations found	Potential Biases	Comments
Cooke 1999 99257637	CP prevalences: 1982-5 (411) 45 10.9% 1986-9 (387) 42 10.9% 1990-3 (398) 29 7.3% P=0.046	ND	No data on funding source
Cooke 1999 99380719	MRI abnormality: VLBW group : 37/87 (42.5%) FT Control group: 0/8 (0%) Abnormal MRI not associated with ADHA, IQ, or motor coordination scores.	No statistical/ data analysis section Few controls (n=8) Disagree and interpretation (i.e. conclusion)	Study was privately funded Overall sample of LBW<2 kg had increased rate of MR compared to gen pop. PVL/VE was independently related to MR (OR 66) and to borderline IQ . Among children with nl IQ, those with PVL/VE vs. no PVL/VE performed more poorly on visual-perceptual organization. White matter injury is associated with adverse cognitive and visual perceptual disability.

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Author, Year	Associations found	Potential Biases	Comments
Finer 1999 99436635	**IVH:** Sample 1: 70%, Sample 2 : 10%, p = .015. **Normal neuromotor outcome**: Sample 1: 70 %, Sample 2: 70%. *Abnormal neuromotor outcome:* Sample 1 : 20%, Sample 2: 0 *Normal developmental outcome:* Sample 1: 80%, Sample 2: 60% *Abnormal developmental outcome:* Sample 1: 20%, Sample 2: 20% *Normal neurodevelopmetal outcome:* Sample 1: 70%, Sample 2 60% No difference in developmental scores of following domains: composite mental, composite motor, adaptive, language, personal/social, fine motor, gross motor. They conclude that intact survival is possible for infants weighting <750 g who received CPR in the DR.	Very small sample size with 28% lost to f/u. Results are from a single center, difficult to generalize the results. Exact criteria for chest compressions and epinephrine not specified No information about the evaluators or whether they were blinded. Infants evaluated at wide range of ages where infants seen later may have done better or worse	No data on funding source Missing information Retrospective collection of breast feeding data

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Futagi 1999 99450356	Predictor evaluation for **CNS outcome**: 1) Birth in surfactant era was not associated with neurodevelopmental outcome (good or poor prognosis) for infants of less than 1000 gms (Pre-surfactant era[107] vs surfactant era [169] • Neurodevelopmental outcome: 71/107 (66%) vs 100/169 (59%) • Cerebral palsy: 13/107 (12%) vs 18/169 (11%) • Mental retardation: 11/107 (10%) vs 16/169 (9.5%) • Borderline intelligence: 11/107 (10%) vs 35/169 (21%) 2) Birth in surfactant era was associated with higher incidence of borderline intelligence (20.6% in surfactant era vs 10.3% in pre-surfactant era) 3) Birth in surfactant era :was not associated with DQ or IQ scores in the individual neurodevelopmental categories (normal neurodevelopmentally, cerebral palsy, mental retardation, borderline intelligence) • Normal: 99.7 vs 100.1 • Cerebral palsy: 57.5 vs 62.5 • Mental retardation: 62.4 vs 55.1 • Borderline intelligence: 77.1 vs 77.6 4) Birth in surfactant era: was not associated with the distribution of subtypes of cerebral palsy.(spastic diplegia, spastic hemiplegia, spastic quadriplegia) 5) Birth in surfactant era was not associated with severity of cerebral palsy.(minimal, mild, moderate, severe)	1) Assessed the association between birth in the surfactant era and neurodevelopmental outcome and not of surfactant administration itself problems of ecological fallacy in that type of studies) 2) It is unknown if the results of this study could be generalized in other NICU populations where more than 50% of infants receive surfactant 3) The possibility of a masked association cannot be excluded due to existence of possible cofounders in the 2 groups. 4) Many subgroup exploratory analyses were performed that were not described in the Method section	Source of funding not reported
Kim 1999 99416608	Infants with BW < 2000g. Assessed at 12 months age. Risk Factor — CP — Devel. Delay — Both CP+DD — Neither Neonatal sepsis — 4/9* — 1/8 — 5/17* — 4/62 BPD — 4/9* — 3/8* — 7/17* — 9/62 IVH > grade 2 — 4/9* — 1/8 — 5/17* — 6/62 Days on ventilator — 18.1 (25.1)* — 11.3 (8.7)* — 12.2 (19.6)* — 3.3 (3.3) Ventriculomegaly — 5/9* — 0 — 5/17 — 8/62 P < 0.05 vs. neither CP/ DD Multivariate logistic regression, the following were not significant risk factors: Apgar score at 5 minutes, BPD, IVH, PDA, duration of mechanical ventilation, Sepsis	Study group as a whole is not described- only those infants developing CP CP infants are compared to "controls", but no description of how the control group was recruited or in what ways they were similar to or different from the study group. Concurrent? Historical? Matched for gestational age or birth weight? We are not told. Leaves open the possibility of massive bias/confounding.	In this cohort of preterm infants (BW 600-1250 grams) <1% blind or deaf; 1%- 3% had seizure disorder; and 7% had CP. Full scale IQ <80 occurred in 28% of total sample (BW 600-1250 grams) at 54 months follow-up

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found				Potential Biases	Comments
Krageloh-Mann 1999 99431017		*MRI normal (n=10)(%)*	*MRI abnormal (n=19)(%)*	*P*	1) Selection of preterm subject bias 2) No MRI of controls 3) Controls, "From Copewnagen suburb"-well matched with regard to SES, health-care measures, etc.? 4) Design is bizarre, complicated, and difficult to interpret. 5) Statistical analysis is not well described. It appears that they did not correct for multiple comparisons, which renders their positive findings suspect. They did not do a power analysis, which renders their negative findings suspect. 6) Much of the paper analyzes association between outcomes evident at 5-7 yrs f/u, for ex., association between abnormal MRI at 5 yr. And IQ at 5 yr.; this does not examine association between neonatal MRI+ IQ at 5 yr.	No data on funding source
	Preeclampsia	50	11	0.03		
	Placental abruption	0	32	0.07		
	Mechanical Ventilation>7d	0	42	0.03		
	ICH grades III + III	0	16	0.53		
	DO2 <ml O2/100g/min	12.5%	63%	0.03		
Salokorpi 1999 99353226	Assessed selected risk factor in relation to cerebral palsy (CP) diagnosed at two years age. CP present, n = 27; CP absent, n = 116. Risk Factor — Odds ratio (CI) Grade 3 or four IVH on head sonogram — 7.94 (2.75, 22.95) Hypotension — 1.26 (0.47, 3.35) Hypocarbia — 2.20 (0.77, 6.31) Also found no association between average duration of ventilation and CP.					Study was privately funded

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Shepherd 1999 99165413	CP 9% in this group of preemies who were followed-up at least once after term age (N=53) Of the 5 infants with CP, 3 had abnormal VEP. Of those without CP, 4 had abnormal VEP. Sensitivity of VEP before term for CP = 60%. Specificity is 92%. Positive predictive value of abnormal VEP for CP is 43%. Negative predictive value is 96%.	CP not defined. CP evaluated by generalists with no uniform definition. Incomplete Methods and large number of missing information.	No data on funding source
Stathis 1999 99325758	Head circumference category at 8 months corrected age related to learning delay greater than one year when assessed at 6 years: HC Category / n / % with delay < 3rd percentile / 23 / 61% (39, 80) 3rd to 10th / 13 / 77% (46, 95) P = 0.004 > 10th / 40 / 30% (17, 47) Head circumference category at 12 months CA did predict McCarthy General Cognitive index at six years, but head circumference category at 24 months CA did not significantly predict McCarthy CGI at 6 years. Head circumference and head growth velocity was not shown to have a relationship with attention deficit hyperactivity disorder. Head circumference category < 10th vs. greater than 10th percentile at four and 8 months corrected age were significantly associated with McCarthy CGI at 6 years age	One nursery High rate of patients lost to follow-up (30%) Small numbers: limited ability to detect small differences; high chances of type 2 error	Study was privately funded

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Vohr 1999 99332101	**Normal Neurologic Examination:** 75% CP overall: 17% but 29% in 401-500 g babies CP (quadriplegia): 6.4% CP (left hemiplegia): 0.45% CP (right hemiplegia): 0.91% CP (diplegia): 8.2% **Seizure disorder**: 5% Hydrocephalus with shunt: 4% Visual impairment (any): 9% Unilateral blindness: 1% overall but 7 % in 401-500g and 801-900g babies **Bilateral blindness**: 2 % overall but 14 % in 401-500 g babies Legally blind in one or both eyes: 3% Hearing impairment: overall 11 % Wearing hearing aids: overall 3 % **Sits unsupported:** 93% Sits well alone: 86% Walks: 83%, Walks fluently: 70% Independently feeds self: 80% **Bayley MDI** < 85 : 66%, Bayley MDI <70: 37% Bayley PDI <85: 57%, Bayley PDI <70: 29% Chronic lung disease, grades 3-4 IVH/PVL, steroids for CLD, NEC, and male gender associated with increased risk for morbidity	Poor f/u rate of 78% and this may significantly underestimate outcome.	

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Agustines 2000 20279724	Predictors for **CNS outcome**: Rates of developmental delay at 30 months of corrected age, were significant among extremely VLBW infants 500-750 g Overall **CNS outcomes** in the 36 infants: 1) Normal MDI: 32% 2) Mild delay in MDI: 40% 3) Severe Delay in MDI: 28% 4) Combined mild and severe delay in MDI: 58% 5) Normal PDI: 42% 6) Mild delay in PDI: 16% 7) Severe delay in PDI: 42% 8) Combined mild and severe delay in PDI: 58%	1) Long term f/up for only 57% (36/63 infants that had survived) Those who had f/up had less morbidity than those lost to f/up (incidence of RDS was 47% vs 92% in lost to f/up group) 2) There was no control group to compare outcomes of extremely VLBW with VLBW infants. 3) Stratified analysis for outcome in different GA subgroups had very few patients in each subgroup, thus the confidence intervals are very wide. 4) This study was not designed to compare outcomes of SGA vs AGA infants in the group of 500-750g: post hoc comparisons (most of the infants in the 26-29 GA group were SGA)	Funding source not report

Stratified by GA:	24 wks (N=14)	25 wks (N=14)	26-29 (N=8)
1) Normal MDI:	11%	50%	33%
2) Mild delay in MDI:	55%	25%	50%
3) Severe Delay in MDI:	33%	25%	17%
4) Combined mild and severe delay in MDI:	88%	50%	67%
5) Normal PDI:	34%	50%	0%
6) Mild delay in PDI:	22%	0%	20%
7) Severe delay in PDI:	44%	50%	80%
8) Combined mild and severe delay in PDI:	68%	50%	100%

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Breslau 2000 20298367	1) Information from mothers and teachers on children's behavior problems at age 11 revealed that the effect of LBW on attention problems differed between urban and suburban settings. 2) LBW children had an excess of attention problems in the urban disadvantaged communities and not in the suburban middle class communities. 3) LBW infants in the urban setting had twice as high incidence of attention problems as more than twice as high in LBW than in NBW. 4) In Urban Setting LBW children had more than 2-fold severe attention problems than NBW children 5) In suburban setting there was no difference in severe attention problems between LBW and NBW children. 6) LBW children had externalizing problems both in the urban and suburban settings (this effect was mainly accounted for by maternal smoking in pregnancy) 7) No LBW effect was observed with respect to internalizing problems 8) Regardless of LBW status, maternal smoking during pregnancy was associated with an increase in externalizing problems 9) No association was found between maternal smoking during pregnancy and internalizing or attention problems OVERALL SCORES — Attention scores — Internalizing — Externalizing MOTHER'S SCORES Urban LBW (n=217) 58.8 52.7 52.2 NBW (n=164) 55.8 51.5 50.4 Suburban LBW (n=194) 55.1 50.4 48.4 NBW (n=142) 53.8 48.6 46.3 TEACHER'S SCORES Urban LBW (n=186) 56.9 50.3 53.9 NBW (n=151) 54.7 48.8 48.5 Suburban LBW (n=180) 53.7 49.0 48.5 NBW (n=135) 54.0 48.7 48.3 1) According to mother's ratings: For attention, externalizing and internalizing problems: LBW scored higher (had more problems) than NBW children. 2) According to teacher's rating: Only for externalizing and internalizing problems: LBW scored slightly higher than NBW. 3) Urban children received higher scores than suburban children on all 3 domains, according to both mother'' and teacher's ratings	1) Recollection bias: The Hx of maternal smoking during pregnancy was elicited when the child was 6 yrs old. This bias would have resulted in underestimation of the confounding effect of smoking during pregnancy. 2) Diagnosis bias: Although there was a correspondence of the findings of teachers' reports (who were blind to the LBW status of children) and the mothers' reports, mothers' reports could have been biased (worse scores from mothers of LBW infants)	Supported by grant from National Institute of Mental Health and National Institute of Drug Abuse

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Buhrer 2000 20280896	Major Neurodevelopmental impairment 22% Independent predictors of neurodevelopmental impairment (logistic regression): CRIB score: R =0.216, ß =0.2233, SE =0.051 Maximum FIO2: R = 0.1201, ß = 1.23, SE 0.4553 Griffith's general quotient = 85 in this population: 21.6%… A CRIB score of 6 or more has a sensitivity and specificity 27.6% and 91.3% for predicting neurologic impairment.	No information as to whether evaluators were blinded	No data on funding source
Grether 2000 20448692	Receipt of MgSO4 treatment: CP (N=170) 98 (58%) Control (N=288) 178 (62%) OR: 0.84 95% CI: 0.56-1.26 Total duration (HR): (mean SD) 51 ± 78 53 ± 72 NS	Retrospective case control CP defined from chart review	No data on funding source
Katz-Salamon 2000 20332284	Infants were assessed at 10 months corrected age. Authors used Griffith's Development Scale and the Movement Assessment Index (MAI, a surrogate for evolving CP) to assess children without high-grade IVH or PVL to determine whether chronic lung disease (CLD) itself was a risk factor for adverse outcomes. CLD was associated with significantly lower performance scores on each Griffith's subscale and with significantly higher MAI scores predicting a higher risk of CP. Even in the absence of high-grade IVH or PVL, CLD has a deleterious effect on early development.	One institution; small number of infants/group Oldest evaluation <10 months of age Used a surrogate measure, the MAI for CP	Study was privately funded Incomplete result data.

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Marlow 2000 20150342	Pulmonary and Other predictors evaluation for **Audiology outcome**. Children with sensorineural hearing loss [15] as compared to control group[30] had longer periods of: 1) Intubation, (14 ds vs 2 ds) 2) Ventilation (34 ds vs 6 ds) 3) Oxygen therapy (57 ds vs 10 ds) 4) Acidosis (12 ds vs 0.5 ds), and 5) More treatments with dopamine (33% vs 7%)or 6) Furosemide (87% vs 53%) 7) Neither P/T of aminoglycosides 8) nor duration of jaundice 9) or level of bilirubin varied between the 2 groups. SNHL was more likely when : 1) netilmicin use coexisted with the peak of bilirubin (87% vs 14%)_ 2) when acidosis occurred when bilirubin was over 200 ?mol/l, (31% vs 4%) 3) when furosemide was used in the face of high creatinine levels (64% vs 27%) 4) when furosemide was used with netilmicin (67% vs 37%) **CNS outcome at 12 mo:** At 12 months of age evidence of cerebral palsy was present in 7/15 (47%) of children with SNHL vs 2/30 (7%) of children without SNHL.(p=0.022)	1) Very small sample size (cases with SNHL only 15) 2) Analyzed too many predictors and combination thereof, for very few outcomes. Very wide confidence intervals; and even those predictors found to be associated with the SNHL this may have been due to chance. 3) The association found between SNHL and cerebral palsy was not based on an adjusted analyses for possible confounders; 4) The 2 groups were different in many factors that were associated with both SNHL and CP	Did not report source of funding
Palta 2000 20096107 (CNS+Eye)	**CP** 12.6%. Independent predictors of CP and functional outcome: IVH OR 2.3 per grade (95 % CI 1.8-2.8) BPD OR 2.3 (95% CI 1.2-4.6) **Percent of the children scoring at least 2 SDs below** the normative means for the following functional outcomes: Self-care 11.7% Mobility 29.5% Social function 10.7%	(None)	Study was government funded No ophthalmology results were reported

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Author, Year	Associations found	Potential Biases	Comments
Torrioli 2000 20275419 (CNS+Eye)	*Movement ABC:* Study: 15.58±7.96 Control: 7.08±4.61 P<0.001 *Bell test rapidity:* Study: 19.08±7.92 Control: 22.02 ± 7.36 P<0.05 *Bell test rapidity:* Study: 57.34±19.67 Control: 69.08 ± 18.10 P<0.05 *Visual function (stereopsis %):* Study: 41.7 Control: 66.7 P<0.05	Did not give the size of the control group. Baseline demographic data not presented.	Study was privately funded
Valkama 2000 20233239	51 BW < 1500g GA <34 wks: Severe CP: 5; Mod CP: 3; mild CP: 1 14 SGA: 2/14 CP (14%) 16 EVLBW<1000g: 6/16 CP (0.34) <29 wks : 12 CP Abnormal MRI 11/19 Delayed myelination 3/8	(None)	Study was privately funded
Vohr 2000 20295211	Studied effect of early IVH at 5 to 11 hours of age on IQ distribution and presence of cerebral palsy (CP). Assessed at 36 months CA. N: Early IVH present 29, Early IVH absent 249 Binet IQ: 78.7 (25) / 87.5 (20) / 0.09 Binet IQ < 70: 38% / 19% / 0.03 PPVT-R: 76.6 (28) / 86.0 (21) / 0.15 CP at 36 months: 25% / 8% / 0.01 Later IVH had effect on Binet IQ similar to early IVH.	IVH rates seems high	No data on funding source

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Dammann 2001 21334215	CP prevalence: BW ≤ 1500g & AGA: 16% BW ≤ 1500g & SGA: 4% P=0.005 In this skewed population, 16 % of AGA infants and 4 % of SGA infants had CP at 6 years.	(None)	Study was privately funded
Gaillard 2001 21221175	Predictors for **Neurodevelopmental outcome:** 1) Shorter length of ventilation (beyond 27(but not 50) postnatal days) was associated with better neurodevelopmental outcome : 59% (33/56) neurodevelopmentally normal or only mildly disabled survivors vs 25% (7/28) with more prolonged ventilation(> 49 ds) *Ventilated beyond 27 (but not 50)ds vs Ventilated beyond 49 ds* Total: 56 vs 28 Survived: 48/56 (86%) vs 14/28 (50% Normal neurodevelopmentally: 26/48 (54%) vs 5/14 (36%) Mild disability: 7/48 (15%) vs 2/14 (14%) Moderate disability: 11/48 (23%) vs 4/14 (29%) Severe disability: 4/48 (8%) 3/14 (21%) *2)* Number of days "off"" ventilator was not associated with the neurodevelopmental outcome at 3 yrs neither in the groups of 27-49 postnatal ds ventilation nor in the group of >49ds ventilation *Ventilated beyond 27 (but not 50)ds and O ds "off" ventilator vs 1-7 ds "off" ventilator vs > 7 ds off ventilator* Total: 18 vs 17 vs 21 Survived: 13 (72%) vs 15 (88%) vs 20 (95%) Neurodevelopmentally normal: 8 (44%) vs 7 (41%) vs 11 (52%) Mild disability: 2 (11%) vs 2 (12%) vs 3 (14%) Moderate disability: 3 (17%) vs 4 (24%) vs 4 (19%) Severe disability: 0 vs 2 (12%) vs 2 (10%) (In the second component: comparison of the retrospective cohort with the historical control) 3) Birth in a period where antenatal steroids and exogenous surfactant was more routinely used was associated with better neurodevelopmental outcome (69% vs 40% and 45% respectively in the 2 historical control cohorts)	In First component: retrospective cases control design: 1) the 2 groups were unmatched for possible confounders, thus cannot exclude false associations 2) Cannot exclude selection bias as only 62 survivors were analyzed from the 84 initially included in the 2 groups In the Second component: 3) Problems of confounders due to historical control group could be even greater Failed to report % of antenatal use in each group. Demographic data included babies that died prior to neurologic evaluation, possible source of bias. No information on comorbidities that may have led to prolonged intubation with no attempt to adjust for these	No data on funding source

Evidence Table 3. Studies Evaluating Association of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Horwood 2001 20574647	Assessed influence of breastfeeding (BF) duration on outcome at 7-8 years age. IQ scores before adjusting for covariates. Group / n / Verbal IQ / Performance IQ Not BF / 76 / 94.4 (18.4) / 98.7 (19.6) BF < 4 mo / 99 / 97.2 (18.4) / 101.4 (15.6) BF 4-7 mo / 46 / 101.7 (17.3) / 101.1 (14.0) BF > 8 mo / 59 / 104.6 (14.7) / 104.9 (15.3) Adjustment for covariates of maternal education, two parent families, higher income families, non-smoking during pregnancy and non-Polynesian ethnicity did not change the hierarchy of results. Verbal IQ beta value = 0.12, P < 0.05 and performance IQ beta value 0.08 with P > 0.15	Retrospective collection of breast feeding data 17 children could not be tested because of sensorineural problems No information about perinatal medical condition Not clear if examiners were aware of feeding history	Study was government funded Goal of study was to assess predictive value of NBRS (neurobiologic risk score) and neonatal neurologic inventory, NNI, with respect to long-term neurodevelopment outcome of preterms between 25-34 weeks.
Nadeau 2001 21163667	EP/ VLBW, n = 61 and controls, n = 44. EP/ VLBW / Control / Significance Normal neuromotor function: 67% / 97% / NS Abnormal neuromotor function: 33% / 3% McCarthy IQ [mean (SD)]: 100.3 (19.1) / 112.8 (16.2) / P < 0.01 Behavioral ratings at 7 years age: Peers rated EP/ VLBW's as significantly more sensitive/ isolated than controls Teachers rated EP/ VLBW's as significantly more inattentive than controls Parents rated EP/ VLBW's as more hyperactive than controls Significantly = P < 0.01	(None)	No data on funding source Data on neuromotor and intellectual functioning only collected once Data on behavior collected once
Pierrat 2001 27221167	Overall, majority of premature infants with cystic PVL are not normal. Cystic-PVL (both Gr II and Gr III) is highly associated with CP. 29 of 30 infants with c-PVL + Ventriculomegaly at 40 wk PMA had CP. The following show differences in outcome based on whether the infant had cystic PVL (Grade II) or cystic PVL (Grade III): c-PVL (Gr II) / c-PVL (Gr III) No motor sequelae: 24% / 3% CP: 76% / 97% Independent walking: 22/29 / 3/26	(None)	No data on funding source

Evidence Table 4. Studies Evaluating Treatment Effects of LBW and Cerebral Palsy and Neurological Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Als 1994 94358983 (CNS+ Pulmonary)	Location: US Years of Birth: ND Median GA (range), wk: Experiment: 27.1±1.6 Control: 26.5±1.4 Median BW (range), g: Experiment: 827±173 Control: : 862±145 Male: Experiment: 45% Control: 61% Race: Black Experiment: 40% Control: 17% SES I, II/III/IV, and V: Experiment: 45%, 20%, 35% Control: 56%, 17%, 27% Enrolled: 43 Evaluated: 38 Number of sites: 1	BW < 1250 g GA < 30 weeks and more than 24 weeks of estimated GA at birth Mechanical ventilation starting within the first 3 hrs after birth and lasting longer than 24 hrs in the first 48 hrs Alive at 48 hrs Absence of chromosomal or other major genetic anomalies, congenital infections, and known fetal exposure to drugs of addiction Singleton At least one family member with some English-language facility Telephone access Living within the greater Boston area	ND	Experiment: VLBW infants participated in individualized developmental care (20) Controls: VLBW infants received standard care (18)	Randomized controlled trial (2 weeks and 9 months)

Evidence Table 4. Studies Evaluating Treatment Effects of LBW and Cerebral Palsy and Neurological Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Corbet 1995 95264244	Location; USA Years of Birth: 1986-1989 Mean GA: Sample 1: 27 ± 2 Sample 2: 27 ± 2 Mean BW: Sample 1: 934 ± 179 Sample 2: 931 ± 191 Males: Sample 1: 50% Sample 2: 50% Race: Sample 1: whites: 41%, blacks: 37%, others: 22% Sample 2: whites: 46%, blacks: 36%, others: 18% Enrolled: 1046 Evaluated: 597 Number of sites: Multicenter	Born alive Qualifying BW (not specified in this publication) That were intubated and assigned randomly to receive either synthetic surfactant or air placebo as part of their participation in 3 multicenter RCTS. Had follow up at 1 yr of age	ND	Sample 1: Synthetic surfactant: [314] Sample 2: Air placebo [283]	Combination of 3 multicenter, randomized, double blind studies of synthetic surfactant vs air placebo [1 yr]

Evidence Table 4. Studies Evaluating Treatment Effects of LBW and Cerebral Palsy and Neurological Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Allan 1997 97336492 Ment 1996 97040638 Ment 2000 20164956 (CNS+All)	Location: US Years of Birth: 1989-1992 Median GA (range), wk: Experiment: 27.7±1.9 Control: 28.4±2.0 Median BW (range), g: Experiment: 945±191 Control: : 988±164 Male: Experiment: 56% Control: 57% Race: ND Enrolled: 505 Evaluated: 431 ? 343 at 36 months ? 337 at 54 months Number of sites: 3	BW 600-1250g Age< 6 hours No IVH presence at 6-12 hours	Died by age of 1 year Lost to follow-up Presence of IVH in sonogram between 6-12 hr of age Bilingual or non–English speaking at home	Experiment Indomethacin group (173) Controls: Placebo (170) At 36 months: Experiment: Indomethacin group (173) Controls: Placebo (170) At 54 months: Experiment: Indomethacin group (170) Controls: Placebo (167)	Randomized Controlled Trial (36, and 54 months)

Evidence Table 4. Studies Evaluating Treatment Effects of LBW and Cerebral Palsy and Neurological Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Van Wassenaer 1997 98103082	Location: Amsterdam Years of Birth: 1991-1993 Mean GA: ND Mean BW: Sample 1/subgr 1: 856 ±153 Sample 1/subgr 2: 1048 ± 195 Sample 1/subgr 3: 1140 ± 156 Sample 1/subgr 4: 1160 ± 246 Sample 2/subgr 1: 914 ± 111 Sample 2/subgr 2: 914 ± 137 Sample 2/subgr 3: 1173 ± 156 Sample 2/subgr 4: 1285 ± 236 Males: Sample 1/subgr 1: 54% Sample 1/subgr 2: 41% Sample 1/subgr 3: 44% Sample 1/subgr 4: 59% Sample 2/subgr 1: 56% Sample 2/subgr 2: 23% Sample 2/subgr 3: 38% Sample 2/subgr 4: 50% Race: ND Enrolled: 200 (100 in thyroxine group and 100 in placebo group) Evaluated: 158 Number of sites: 1	Premature : 25-30 wks Admitted to their NICU within first 24 hrs of life Admitted between 1991-1993	Congenital malformations Maternal endocrine disorders Maternal illicit drug use	Sample 1 Thyroxine (8 ?g/kg BW once daily) for the first 6 wks of life starting during the first 12-24 [82] Subgroup 1: 25-26 GA [13] Subgroup 2: 27 GA [17] Subgroup 3: 28 GA [23] Subgroup 4: 29 GA [29] Sample 2: Placebo [76] Subgroup 1: 25-26 GA [18] Subgroup 2: 27 GA [13] Subgroup 3: 28 GA [21] Subgroup 4: 29 GA [24]	Prospective comparative study (The initial study was a randomized, double blind, placebo-controlled trial but in the current comparative component the patients in the subgroups of different GA that were compared were no longer randomly assigned)

Evidence Table 4. Studies Evaluating Treatment Effects of LBW and Cerebral Palsy and Neurological Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
O'Shea 1999 99318938	Location: Korea Years of Birth: 1992-1995 Median GA (range), wk: Experiment: 25 (23-29) Control: 26 (23-31) Median BW (range), g: Experiment: 747 (420-1362) Control: 775 (495-1324) Male: Experiment: 48% Control: 51% Race: African-American Experiment: 34% Control: 49% Enrolled: 118 Evaluated: 95 Number of sites: 2	BW < 1501 g Age 15-25 days old Not wearing ventilator, no sepsis; no PDA , an echocardiogram indicating the absence of a patent ductus arteriosus	Parental refusal Survived to 1-year adjusted age	Experiment Dexamethasone x 42 days (50) Controls: Placebo (45)	Randomized controlled trial (1 year)

Evidence Table 4. Studies Evaluating Treatment Effects of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Als 1994 94358983	Other: Participation in individualized developmental care staffing by specially educated nurses	The psychologist and clinical nurse specialist provided ongoing support for the care teams and parents of the infants in the experimental group in jointly planning and implementing individually supportive care and environments.	**CNS:** Neurodevelopmental: Cognitive delay **Pulmonary:** BPD severity	Baley Scale of Infant Development at 9 months of age Assessed by double-blind review of cranial US scans by a consultant senior radiologist

Evidence Table 4. Studies Evaluating Treatment Effects of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Corbet 1995 95264244	General: 1) Synthetic surfactant (single dose via ET tube of 5 mg/kg vs air placebo)	Not further specified	**Growth:** Growth status at 1 yr: 1) Weight 2) Height, 3) HC and percentiles distribution **Other:** Health status at 1 yr: 1) Surgeries 2) Readmissions to hospital 3) CLD, medications for CLD 4) Respiratory support on exam day 5) Medications for chronic neurologic disease 6) Asthma, Eczema **CNS:** Neurodevelopmental outcome 1) MDI 2) PDI 3) Impairments: Present absent 4) Severity of impairment 5) Type of impairment (MDI<69, MDI 69-84) 6) CP **Audiology** 1) B/L sensorineural deafness 2) Deafness not requiring amplification **Ophthalmology:** (worst exam and last) 1) B/L blindness 2) Visual defect 3) No ROP, mild/moderate ROP, severe ROP) 4) Treatment for ROP (surgery, cryotherapy)	Assessment at 1 yr of corrected age Not further specified

Evidence Table 4. Studies Evaluating Treatment Effects of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Allan 1997 97336492 Ment 1996 97040638 Ment 2000 20164956 (CNS+All)	General: SGA/IUGR, Antenatal steroids; Apgar score, Gender CNS : Intracranial/Intraventricular hemorrhage Indomethacin Seizures Indomethacin Pulmonary: bronchopulmonary dysplasia Other: multiple birth, MgSO4, Surfactant	Diagnoses according to radiologic assessments. The grading system for hemorrhages was: grade 1, blood in the periventricular germinal matrix regions; grade 2, blood within the lateral ventricular system without ventricular dilation; grade 3, blood within and distending the lateral ventricles; and, grade 4, blood within the ventricular system and parencyhmal involvement.	**CNS:** Cerebral palsy Neurodevelopmental: Cognitive delay Mental retardation Behavioral Disorders Seizure disorder **Ophthalmology**: Blindness **Audiology:** Deafness	Neurologic examination <u>At 36 months</u>: Stanford-Binet IQ PPVT-R <u>At 54 months</u>: Cognitive delay: WPPSI-R or PPVT-R (Full scale IQ<70) Vineland adaptive checklist and child behavior checklist

Evidence Table 4. Studies Evaluating Treatment Effects of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Van Wassenaer 1997 9810382	Other/General: 1) Thyroxine administration during first 6 weeks of life (vs placebo) 2) GA	Thyroxine administration started at 12-24 hrs of life in a fixed dose of 8 ?g/kg BW, once daily	**CNS** 1) Neurologic outcome 2) Developmental outcome (Assessment at 24 mo corrected age)	Neurodevelopmental outcome: Described in another publication Abnormal if: 1) Severe abnormality of tone 2) Severe abnormality of posture 3) Severe abnormality of movement Leading to functional impairment or Delay in motor development Suspect if: 1) Moderate abnormality of tone 2) Moderate abnormality of posture 3) Moderate abnormality of movement Leading to mild or moderate functional impairment or developmental delay MDI (Mental Development Index by Bayley) PDI (Psychomotor development index by Bayley) According to Dutch standards 1) Abnormal if: < 2 SDs below mean Or if score< 68 2) Suspect if < 1 SD or score: 68-84 3) Normal if score> 83

Evidence Table 4. Studies Evaluating Treatment Effects of LBW and Cerebral Palsy and Neurological Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
O'Shea, 1999 99318938	Other: Dexamethasone	ND	**CNS:** CP Neurodevelopmnetal: Cognitive delay Neurological exam	CP was diagnosed only if both a pediatrician and a physical therapist agreed with impaired motor function Bayley scale Based on subjective assessment of the physician and therapist, the neurologic exam was classified into no, mild, moderate, and severe abnormality. "Mild abnormality" – hypotonia (which typically was most prominent in the truncal musculature) but not CP No definition for moderate and severe abnormality.

Evidence Table 4. Studies Evaluating Treatment Effects of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found				Potential Biases	Comments
Als 1994 94358983	Studied effect of an individualized developmental care plan on Bayley score at 9 months age and occurrence and severity of BPD.				Small number of babies studied Only one NICU Only one neurodevelopmental assessment at 9 months of age Reported timing of IVH different from many other studies High potential for contamination	Study was government funded
		Experimental group	Controls	P value		
	N	20	18			
	Bayley MDI	118.30 (17.35)	94.38 (23.31)	< 0.001		
	Bayley PDI	100.6 (20.19)	83.56 (17.97)	< 0.01		
	No BPD	2/20	3/18			
	Mild BPD	13/20	7/18			
	Moderate BPD	5/20	2/18			
	Severe BPD	0	6/18	0.03		

Evidence Table 4. Studies Evaluating Treatment Effects of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Corbet 1995 95264244	**GROWTH** AT 1 YR: Mean measurements of Height (74 cm), weight (9.1 kg) and HC (46 cm) and growth percentiles were equivalent in the 2 groups. **HEALTH STATUS** AT 1 YR: No difference in parameters between 2 groups 1) Surgeries (33% vs 34%) 2) Readmission to hospital (45% vs 39%) 2) CLD (11% vs 10%) 4) Medications for CLD (14% vs 14%) 3) Respiratory support (4% vs 2%) 4) Med. for chronic neurologic problems (1% vs 2%) 5) Asthma (this only was s/s : 9% vs 3%) 8) Eczema (2% vs 1%) **NEURODEVELOPMENTAL OUTCOME:** No difference in the outcomes between the 2 groups in these parameters. 1) Mean MDI (values <50= 49): 2) Mean MDI (only children with MDI>69) 2) Number of children with MDI<69: 4) Number of children with PDI<69 3) Mean PDI (values<50=49) 6) Mean PDI (only children with PDI>69) **CNS IMPAIRMENT:** No difference in any impairments between 2 groups 1) Present: 43% vs 37% 2) Absent: 57% vs 63% 2) Mild/moderate: 20% vs 14% 4) Severe:23% vs 23% 3) MDI<69: 17% vs 16% 6) MDI: 69-84: 18% vs 14% 4) CP mild: 8% vs 7% 8) CP moderate/severe: 7% vs 7% **Audiology:** 1) B/L sensorineural hearing deafness: 0% vs 1% 2) Deafness not needing amplification: 0% vs 1% **Ophthalmology:** 1) B/L blindness: 3% vs 2% 2) Visual defect: 8% vs 8% Worst examination 2) No ROP: 30% vs 33% 2) Mild/moderate ROP: 53% vs 52% 3) Severe ROP: 17% vs 15% 4) Surgical treatment for ROP:10% vs 12% 4) Cryotherapy for ROP: 5% vs 6% Last examination 5) No ROP: 69% vs 72% 2) Mild/moderate ROP: 26% vs 22% 6) Severe ROP: 5% vs 6% 4) Surgical treatment for ROP: 4% vs 4% 7) Cryotherapy for ROP: 2% vs 3% Infants who survived after treatment at birth with single-dose synthetic surfactant fare as well in terms of growth, development and late morbidities as infants who survive without treatment. No difference in medical history during first year of life, growth, incidence of visual or auditory defects, CP, neurodevelopmental delay at 1 yr adjusted age.	1) The incidence of severe impairment in the 19% of infants who did not return for evaluation at the age of 1 yr may be higher than in those who were evaluated.	Source of funding not reported. 1) The neurodevelopmental evaluation of infants at 1 yr may not be absolutely reliable for the estimation of later outcome. 2) The estimated mental retardation is likely to be low, and the estimated CP is likely to be high, compared to estimates at 2 and 3 yrs.

Evidence Table 4. Studies Evaluating Treatment Effects of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Allan 1997 97336492 Ment 1996 97040638 Ment 2000 20164956 (CNS+All)	Antecedents of Cerebral Palsy (CP). Risk Factor — n — Percent with CP — P value BPD Yes 177 15% No 203 4% < 0.001 Surfactant Yes 245 13% No 136 4% 0.003 Grade 3 or 4 IVH Yes 15 53% No 366 8% < 0.001 PVL Yes 25 53% No 352 6% < 0.001 Ventriculomegaly Yes 17 59% No 328 7% < 0.001 Assessed at 36 months corrected age: No significant differences between placebo and indo. for: Presence of CP/ abnormal neurologic exam (8% vs. 8%, Placebo vs. Indo); Blindness (1% in each); Deafness (1% in each); Stanford-Binet IQ (85.0±20.8 vs. 89.6±18.9, Placebo vs. Indo) Presence of IVH was associated with a significant decrease in Stanford-Binet IQ: IVH absent, 84.4 ± 19.6 vs. IVH present 80.2 ± 20.9 (P = 0.03) Assessed at 54 months corrected age: Indomethacin — Placebo — P-value N 170 167 Blind 1 (<1%) 1 (<1%) ns Deaf 1 (<1%) 1 (<1%) ns Seizures 1 (1%) 5 (3%) ns CP 7% 7% ns WPPSI Full IQ<70 9% 17% 0.035 WPPSI Full IQ 70-80 12% 18% PPVT-R IQ<70 12% 26% 0.02 PPVT-R IQ70-80 19% 6% N 119 114 Vineland Total Score *There was no significant difference between groups: Communication; Daily living skills; Socialization; Motor skills For CBCL results, children in Indo. group has significant lower score in Withdrawn subscale than children in Placebo group (52.7 vs. 54.6, p=0.02). There is no significant difference found in the other subscales of CBCL.	Stanford-Binet testing limited to monolingual, English-speaking families	Study was government funded Study in a follow-up of originally randomized cohort; followed at 36 and 54 months age, corrected

Evidence Table 4. Studies Evaluating Treatment Effects of LBW and Cerebral Palsy and Neurological Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Van Wassenaer 1997 9810382	1) In infants of 25-26 wks GA, thyroxine administration during the first 6 weeks after birth is associated with an improvement in mental developmental outcome/MDIs.($p<0.01$) 2) Thyroxine administration does not improve and might even harm mental (but not psychomotor/PDIs or neurological) outcomes in infants 27-20 wks. 3) There was also a trend towards a better psychomotor and neurologic outcome (normal, suspect, abnormal).	1) In this study, many pot hoc exploratory subgroup analyses were done: Small number of patients in each subgroup and although the patients were randomly assigned in the original 2 groups, this does not continue to be the same for the subgroups of different GA analyzed. 2) Thus association proposed for beneficial effect of T4 particularly for the subgroup of infants less than 27, weeks and only for the MDI scores; and not for the PDI scores or the neurological outcomes; must be viewed cautiously. 3) Except for Thyroxine and GA the effect of the other covariates/predictors included in the linear regression model was not discussed.	It should be taken into consideration that the initial RCT with 200 infants less than 30 wks had shown no clear association between thyroxine administration and neurodevelopmental outcome.
O'Shea, 1999 99318938		(None)	Study was government funded

	Dexamethasone (N=50)	*Placebo (N=45)*	*P*
Definite Cerebral Palsy:	12	3	
Possible CP:	5	2	
Overall CP:	17	5	0.006
Neuro exam severe Abnormal:	4	2	
Mild abnormal:	16	6	
Overall abnormal Neuro exam:	20	8	0.03

Evidence Table 5A. Studies Evaluating Association of LBW to Speech and Language Disorders
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Wood 2000 20373840	Location: UK and Ireland Years of Birth: 1995-1996 Mean GA (range), wk: 22-25 Mean BW (range), g: ND Male: ND Race: ND Enrolled: 314 Evaluated: 283 Number of sites: 276	GA 20-25 weeks survivors	ND	Preterm infants (283)	Prospective cohort (30 [28-40] months)
Lefebvre 1998 98387703	Location: Canada Years of Birth: 1987-1992 Mean GA (range), wk: 27.0±1.2 Mean BW (range), g: 961±179 (585-1450) Male: 52% Race: ND Enrolled: 139 Evaluated: 121 Number of sites: 1	GA<28 weeks 3 or more cranial ultrasounds Survival to discharge	ND	Preterm infants (121): Low risk (50) Moderate risk (37) High risk (34)	Prospective cohort (CA 18.6±1.2 [17-19] months)

Evidence Table 5A. Studies Evaluating Association of LBW to Speech and Language Disorders
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Wolke 1999 10075095	Location: Germany Years of Birth:1985-1986 Description of group: Sample 1: VLBW Sample 2: Full term/ controls Sample 3: Normative sample Mean GA (range), wk: VLBW: 29.5± .2 (29.3-29.7) Control: 39.6± .1 (39.5-39.7) Mean BW (range), g: VLBW: 1288±42 (1247-1330) Control: 3407±58 (3351-3463) Male (%): VLBW: 56.4% Control: 56.4% Normative: 51% Race: ND Enrolled: VLBW: 560 Control: 916 Normative: 311 Evaluated: VLBW: 264 Control: 264 Normative: 311 Number of sites: 17 (hospitals)	Cases: 1) Requiring admission to 1 of 17 hospitals in S. Bavaria within first 10 days. 2) Assessments at 5 and 20 months, 4 years 8 months, and 6 years 3 months. 3) VLBW (very preterm) GA≤ 32 weeks at birth. Controls: 1) Control group (full term) GA>36 weeks at birth. For all groups: German-speaking	ND	Cases: Sample 1: VLBW (or very preterm): 264 Controls: Sample 2: Full term/ controls: 264 Sample 3: Normative: 311	Non-randomized comparison trial

Evidence Table 5A. Studies Evaluating Association of LBW to Speech and Language Disorders
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Smith 1996 97081985	Location: US Years of Birth: 1990-1992 Description of group: Sample 1: High risk VLBW Sample 2: Low risk VLBW Sample 3: Full term (controls) Mean GA (range), wk: HR VLBW: 28± 2 LR VLBW: 30.9±2 FT: 39.1±5.9 Mean BW (range), g: HR VLBW: 930±233 LR VLBW: 1263±202 FT: 3187±767 Male (%): HR VLBW: 50% LR VLBW: 41% FT: 50% Race (% African-American): HR VLBW: 57% LR VLBW: 62% FT: 62% Enrolled: HR VLBW: 89 LR VLBW: 123 FT: 128 Evaluated: HR VLBW: 88 LR VLBW: 123 FT: 128 Number of sites: 2	Cases: 1)VLBW≤1600 g 2)Female primary caregiver 3)Completed both a 6 and 12 mos. home visit. 4)GA≤ 36 weeks at birth. Sample 1: HR VLBW: one or more severe medical complications: bronchopulmonary dysplasia (BPD) defined as need for O_2 for more than 28 days, severe IVH with progressive dilitation defined as a Grades III or IV subependymal hemorrhage, and/or periventricular leukomalacia characterized by ischemic lesions. Sample 2: LR VLBW: one or more less severe medical complications, including transient respiratory distress where O_2 is required for less than 28 days and/or mild IVH without dilitation- Grades I and II. Controls: Sample 3: FT: GA: 37-42 weeks with normal pregnancy history and physical examination at birth.	1) Primary caregiver age<16, drug abuser, or not English-speaking. 2) Sensory impairment, meningitis, encephalitis, congenital syphilis, congenital abnormality of the brain, cardiac abnormalities, NEC or HIV antibody positive.	Cases: Total VLBW: 211 Sample 1: HR VLBW: 88 Sample 2: LR VLBR: 123 Controls: Sample 3: Full-term infants: 128	Non-randomized comparison trial

Evidence Table 5A. Studies Evaluating Association of LBW to Speech and Language Disorders
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Sajaniemi 2001 11227991	Location: Finland Years of birth:1989-1991 Description of group: VLBW Mean GA (range), wk: 29.4± 3 Mean BW (range), g: 1246±472 Male: ND Race: ND Days of mechanical ventilation: 12.3±26 Enrolled: 138 Evaluated: 63 Number of sites: 1	Cases: 1) Mothers referred to University Central Hospital in Helsinki for threatened pre-term delivery 2) Assessments at 2 and 4 months, 3) VLBW (very preterm) GA≤ 29.4± 3 weeks at birth.	Major disabilities (CP or mental retardation)	Cases: VLBW (or very preterm): 63 No control group	Prospective (single arm) cohort
Briscoe 1998 98300800	Location: UK Years of Birth: 7/91- 7/92 Mean GA (range), wk: 28±1.9 (26-32) Mean BW (range), g: 1206±345 (815-1985) Male: ND Race: ND Enrolled: 26 (26 controls) Evaluated: 26 (26) Number of sites: 1	Cases: Preterm infants, GA<32 weeks, from an Avon Premature Infant Project, Marlow, 1997. Free of major and minor physical impairment at 2 years of age Controls: Children age between 3years 7 months and 4 years 5 months born full-term, GA>37 weeks.	ND	Cases: Preterm infants (26) Controls: Full term infants (26)	Case-control study

Evidence Table 5A. Studies Evaluating Association of LBW to Speech and Language Disorders
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Saigal 2001 21376729	Location: Canada Years of Birth: 1977-1982 Mean GA (range), wk: Cases: 27±2 Controls: "Term" Mean BW (range), g: Cases: 835±124 Controls: 3401±481 Male: Cases: 31% Controls: 36% Race: ND SES: middle class Cases: 30% Controls: 30% Enrolled: 179 (145 controls) Evaluated: 154 (125) Number of sites: 1	ELBW survivors, BW= 501-1000g Controls: term infants recruited at 8 years of age from a random list obtained through the directors of 2 school boards and matched for gender, age, and SES to each case	ND (Died after discharge (10) Lost to follow-up (8) Refusal (5) Unable to be reached (2) Controls: Lost to follow-up (10) Refusal (8) Unable to be reached (2))	Cases: ELBW infants (154) Controls: Term infants (125)	Prospective cohort (followed to 12-16 years age)

Evidence Table 5A. Studies Evaluating Association of LBW to Speech and Language Disorders
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Schendel 1997 98033417	Location: US Years of Birth: 12/1/89 to 3/31/91 Mean GA (range), wk: Sample 1: 28.4 ±3.0 Sample 2: 35.6 ±2.8 Controls: 39.4 ±1.5 Mean BW (range), g: Sample 1: 1088±268 Sample 2: 2184±267 Controls: 3417±432 Male: Sample 1: 49% Sample 2: 46% Controls: 52% Race: Black Sample 1: 37% Sample 2: 37% Controls: 41% Enrolled: 920 (555 controls) Evaluated: 920 (555) Number of sites: 5	Singleton livebirths in MMIHS study population, survived to 1 year of age Cases: MLBW infants, BW 1500-2499g; VLBW infants, BW<1500g Controls: NBW infants randomly selected from the birth certificate files on the basis of frequency matching with cases by maternal race, age, and residence	ND	Sample 1: VLBW infants (367) Sample 2: MLBW infants (553) Controls: NBW infants (555)	Case-control study

Evidence Table 5A. Studies Evaluating Association of LBW to Speech and Language Disorders
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Singer 2001 21163669	Cardiovascular or pulmonary predictors: 1) Bronchopulmonary dysplasia General : BW, Neurologic risk Other: Race, Socioeconomic status	BPD: preterm,<1500g BW, oxygen for >28 days with radiographic evidence of CLD	**CNS outcomes:** Cerebral palsy Cognitive delay Mental retardation **Ophthalmology outcomes:** Visual impair ment **Audiology outcomes:** Hearing disorders Speech Language Communication disorder	Bayley scale of infant development Language (speech/communication) measured by Battelle Developmental Communication Subscale Domain→ receptive, expressive and total communication scores converted to DQ mean 100 and SD 15.
Wood 2000 20373840	*General:* 1) GA 2) Gender Other: Perinatal Factors→ Multiple gestation	ND	**CNS:** Motor delay Cognitive delay Seizure disorder Overall development **Ophthalmology:** Visual impairment Blindness **Audiology:** Hearing disorders Deafness Speech Communication disorder **Other:** Severely disabled Other disability No disability Disability of hearing, vision, or communication	Bayley scales Severe disability = need of physical assistance to perform daily activities. If disability didn't fit into this category = "other disability"

Evidence Table 5A. Studies Evaluating Association of LBW to Speech and Language Disorders
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Lefebvre 1998 98387703	Other: Neurobiologic risk score (NBRS)	Items in NBRS: ventilation, PH, surgeries, IVH< PVL, infection, hypoglycemia-items scored zero or greater in progression	**CNS:** Cerebral palsy Cognitive delay- Other: neurodevelopmental impairment **Ophthalmology**: Blindness **Audiology:** hearing disorders-free fetal audiogram	Neurologic exam Griffith's mental development scale Mental retardation-Griffith's mental development scale 1) Global developmental quotient (DA) 2) Mild/moderate: DA 80-89 or CP 3) Severe: DA<80, severe CP unilateral blindness or severe hearing defect 4) Normal: more of the above Areas of Griffith's Developmental Scales: - Locomotor - Personal-social - Hearing and speech - Eye and hand coordination - Performance Control mean DA=110+or- in literature

Evidence Table 5A. Studies Evaluating Association of LBW to Speech and Language Disorders
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Wolke 1999 10075095	General predictors: GA	Gestational age GA≤32 for VLBW, GA>36 weeks for full term control group.	Audiology outcomes: 1) Language development 2) Prereading skills 3) Cognitive status	I. <u>Language development</u> a) Heidelberger Sprachentwicklungstest (HSET) (German test) II. <u>Prereading skills:</u> a) Rhyming and sound-to-word-matching tasks III. <u>Cognitive status</u>: a) Kaufman Assessment Battery for Children (K-ABC) for cognitive assessment. Intelligence was measured with the Mental Processing Composite (MPC): simultaneous and sequential information processing subtests (SGD and SED), and The Achievement Score (AS)
Smith 1996 97081985	General predictors: Illness acuity, grouped into LR VLBW and HR VLBW, and maternal behavior, warm sensitivity and maintaining of infants interests and directiveness.	Gestational age GA≤ 36 weeks at birth.	Audiology outcomes: 1) Cognitive skills 2) Language development 3) Living skills	I. <u>Cognitive skills</u>: a) Bayley Scales of infant Development expressed as mental age II. <u>Language development:</u> a) Sequenced Inventory of Communication Development III. <u>Living Skills</u>: a) Daily Living Skills subscale from the Vineland Adaptive Behavior Scale

Evidence Table 5A. Studies Evaluating Association of LBW to Speech and Language Disorders
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Sajaniemi 2001 11227991	General predictors:	Gestational age GA≤ 29.4± 3	Audiology outcomes: 1) Temperamental characteristics (at 2 years of age) 2) Behavioral characteristics (at 2 years of age) 3) Cognitive precursors (at 2 and 4 years of age) 4) Neuropsychological assessment (at 4 years of age)	I. <u>Temperamental characteristics:</u> a) Toddler Temperament Questionnaire (TTQ), measuring activity, rhyhmicity, approach, adaptability, intensity, mood, persistence, distractability, and sensory threshold. II. <u>Behavioral characteristics</u>: a) Infant Behavior Record (IBR) of the Bayley Scales, measuring fearfulness, emotional tone, activity, attention span, and goal directness. III. <u>Cognitive precursors:</u> a) Mental Development Index (MDI) from the Bayley Scales of Infant Development was used to measure cognitive level at 2 years. a) Wechsler Preschool-Primary Scale of Intelligence (WPPSI) (Finnish version) was used at 4 years of age. IV. <u>Neuropsychological assessment:</u> a) pre-standard version of the Finnish Neuropsychological Investigation for Children (NEPSY-r, extended version)

Evidence Table 5A. Studies Evaluating Association of LBW to Speech and Language Disorders
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Briscoe 1998 98300800	General predictors: GA	Gestational age < 32 weeks based on expected date of delivery	Audiology outcomes: 1) Language 2) Short-term memory 3) General non-verbal ability	II. Vocabulary knowledge: a) British picture vocabulary scales b) Oral vocabulary component of McCarthy scales of Children's Abilities c) Bus Story test of Continuous speech tested expressive language ability (retelling story using pictures as on aid) III. Phonological short-term memory: a) Digit span: set of pseudo-random numbers to repeat b) Non-word repetition IV. Non-verbal ability: a) Raven's Progressive Coloured Matrices adapted for use here under 5 years of age V. Early Development Assessment a) Griffith's mental development scales

Evidence Table 5A. Studies Evaluating Association of LBW to Speech and Language Disorders
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Saigal 2001 21376729	Birth weight GA	ELBW=500-1000 g	**CNS:** Motor delay Cognitive delay Other: neurosensory impairment **Ophthalmology:** Visual impairment **Growth:** Height Weight Head circumferences BMI (wt/ht2) **Other:** Health status and problems; current and past Extra health care expenses Utilization and health care resources	Reported previously in the authors' other paper Growth reference population was using the age- and gender-specific reference data provided by the NCHS growth chart
Schendel 1997 98033417	**General Predictors** 1) Birth Weight- 3 groups VLBM (very low birth wt) MLBW (moderately low birth wt.) NBW (normal birth wt) **Other Predictors** *1)* Other: married at birth *2)* Other: Medicaid recipient	ND	**CNS:** Other: Developmental Delay **Pulmonary:** Birth weight	Developmental delay measured by Denver Developmental Screening Test II. "DELAY" defined by 9 measures of performance on Denver Developmental Screening Test II at age 15 months corrected.

Evidence Table 5A. Studies Evaluating Association of LBW to Speech and Language Disorders
Part III

Author, Year	Associations found	Potential Biases	Comments
Singer 2001 21163669	Evaluation at 36 months corrected age. VLBW, VLBW with BPD, full term (FT). Bayley MDI / % with MDI below 70 VLBW 90 ± 16 (38-126) 11% VLBW w/ BPD 84 ± 24 (10-116) 21% FT 96 ± 12 (57-127) 4% P = 0.001 for VLBW vs. VLBW w/ BPD Bayley PDI / % with PDI below 70 VLBW 98 ± 20 (33-122) 9% VLBW w/ BPD 84 ± 29 (8-127) 9% FT 103 ± 15 (58-128) 1% P = 0.001 for VLBW vs. VLBW w/ BPD At 3 years BPD predicted poorer motor outcome but not poorer mental outcome. **Receptive DQ**: BPD < VLBW < Term, p < 05 **Receptive DQ < 85:** BPD 49%, VLBW 34%, Term 30%, BPD < VLBW + Term p < .05 **Expressive DQ:** BPD < VLBW + Term, p < .05 **Expressive DQ<85:** BPD 44%, VLBW 25%, Term 25% BPD < VLBW + Term p < .05 **Communication DQ**: BPD < VLBW + Term, p < .05 **Communication DQ < 85:** BPD 43%, VLBW 31%, Term 28%, NS Rank order listing of risk factors in order of magnitude of effect and the number of communication DQ lowered by the risk factor: PDA lowered DQ by 13 points, Minority race by 6 points, lower socioeconomic status by 5 points, and higher neurologic risk by 5 points. p .001 **Bayley Scales MDI:** BPD 83.7 ± 24, VLBW 90 ±16, Term 96.4 ± 12, BPD < VLBW < Term, p< 0.05 **Bayley Scales PDI:** BPD 84.1 28, VLBW 97.4 19, Term 102.8 14 BPD < VLBW + Term, p< .05 **ROP:** BPD 43%, VLBW 4%, p= .001 **Seizures**: BPD 7%, **Neurologic score**: BPD 1.3 ± 2, VLBW 58 ± 1, p < .001	Single region, but at least it is a region Unclear if examiners were blinded to groups' status	Study was government funded
Wood	Infants 22-25 weeks GA developmentally assessed at median 30 months	(None)	Severe disability common

Evidence Table 5A. Studies Evaluating Association of LBW to Speech and Language Disorders
Part III

Author, Year	Associations found	Potential Biases	Comments
2000 20373840	• 138/283 had disability (49%:64 met criteria for severe disability) • 49% no disability • 53/283 severely delayed 19%(Bayley below 3 SD) • 32/283 2-3 below SD 11% • 28 severe neuromotor disability 10%; 7 blind or perceived light only 2% • 8 hearing loss that was uncorrectable or required hearing aids 3% Survived without overall disability 22 wks----------0.7 % 23 wks----------5% 24 wks----------12% 25 wks----------23% Severe disability at 30 months 22 ----------0.7% 23 ----------3% 24----------6% 25----------9% • no relation between morbidity pattern and either gestational age &multiple birth; boys were likely to be disabled than girls		Children born extremely premature
Lefebvre 1998 98387703	Assessed at 18 months corrected age. Divided into low, moderate and high risk group based on Neurobiologic risk score (NBRS). Tested with Griffith's Developmental Scales. Griffiths Developmental Score Category Risk Group n Severe impairment, <80 All < 80 Low 50 0% 12% Moderate 37 22% 24% High 34 50% 71% Significance: for severe or any delay the NBRS was predictive, P < 0.0001 Risk Group n Severe CP (+) Any CP Low 50 0% 4% Moderate 37 13% 19% High 34 26% 41% Significance: NBRS predictive of CP, severe CP, P < 0.0009, any CP P < 0.0001	(None)	Study was privately funded
Wolke	• Preterm birth is significantly associated with deficits in wide range of	Drop-out rate <25%.	Internal validity: A

Evidence Table 5A. Studies Evaluating Association of LBW to Speech and Language Disorders
Part III

Author, Year	Associations found	Potential Biases	Comments
1999 10075095	abilities including all measures of cognition, language comprehension and expression, articulation, and prereading skills compare to full-term controls. • Specific intellectual deficit is in simultaneous central information processing • Specific language deficits include problems with grammatical rules, detecting semantically incorrect sentences, motor aspects of speech, articulation, and pronunciation • Specific prereading skills deficits include problems with rhyming tasks, sound-to-word matching and naming or number/letters. • Deafness 0% in the preterm group		
Smith 1996 97081985	• HR infants have a significantly lower mental age (cognitive skills) at 6 and at 12 mos. then either FT controls or LR infants. • HR infants scored lower in living skills at 6 mos. than FT's but not LR infants. There was no difference between groups at 12 mos. • HR infants scored lower for language development at 6 and 12 mos. than FT controls	The overwhelming majority of HR VLBW's were HR because of BPD with or without IVH. Low socioeconomic status, inner city population	Study was privately funded
Sajaniemi 2001 11227991	• Cognition, behavior and temperament as early as 2 year of age predicted impaired language functioning at age 4 years in infants without major disabilities. • Preterm children were temperamentally less active, less persistent, and less goal-directed with passive attitude toward environmental stimulus. • Preterm infants were less cooperative and highly distractable.	No full-term controls	Internal validity B
Briscoe 1998 98300800	When comparing short-term memory and language outcomes, across all measures, preterm infants performed at a lower level, typically one half SD lower. • 2/3 of preterm infants had normal cognitive profiles. • "at risk" subgroup of preterms for language impairment can be identified using an expressive screening tool at an early age (less than 5 yrs) when intervention can be effective(Bus Story Test). • Meta-analysis 80 studies, preterm IQ lower than full terms but still in the normal range.	No difference in regard to social class, maternal education or single parent status. No GA less than 26 weeks Small sample made effect of IVH/PVL difficult to interpret "Most" children were recruited through friends and relatives (excluding siblings) of the preterm children in order to minimize social and economic disparity	Study was privately funded
Saigal 2001	Neurosensory Impairment:: ELBW 28%, FT Controls 2%, p= 0.001 Growth: Weight: diff. between ELBW and FT (mean z scores) –5.78	Didn't specify exclusion criteria but these are implied based on clear industry criteria units;	Study was privately funded

Evidence Table 5A. Studies Evaluating Association of LBW to Speech and Language Disorders
Part III

Author, Year	Associations found	Potential Biases	Comments
21376729	(p<0.0001) Visual Problems: ELBW 57%, FT Controls 21%, p=<0.001 (OR 5.1, CI 2.89-9.05) Current Health Problems (multiple/patient): ≥3 Health Problems: ELBW 35%, FT Controls 7%, p<0.0001 Past Health Problems: Seizures: ELBW 11%, FT Controls 2%, p<0.005 Asthma: ELBW 25%, FT Controls 14%, p=0.05 Recurrent bronchiolitis/pneumonia: ELBW 14%, FT Controls 3%, p=0.005 Current (at 12-16 yr age) Functional Limitation (Table 4 page 411) (multiple/patient) Visual difficulty: ELBW 57%, FT Controls 21%, p<0.001 Hearing Difficulty: ELBW 7%, FT Controls 5%, ns. Emotional problems: ELBW 4%, FT Controls 1%, ns Mental problems: ELBW 4%, FT Controls 1%, ns. Clumsiness: ELBW 25%, FT Controls 1%, p<0.001 Developmental Delay: ELBW 26%, FT Controls 1%, p<0.001 Learning Disability: ELBW 34%, FT Controls 10%, p<0.001 Hyperactivity: ELBW 9%, FT Controls 2%, p=0.04 Reduced self-abilities: ELBW 5%, FT Controls 0%, p=0.02 Limitation in school or in normal activity: ELBW 31%, FT Controls 9%, p<0.002 Any functional limitation: ELBW 81%, FT Controls 42%, p<0.001 Functional limitation/child [Mean (SD)]: ELBW 2.0 (1.8), FT Controls 0.6 (0.8), p<0.001 Utilization of Health Care Resources: Pediatrician: ELBW 34%, FT Controls 14%, p<0.0002 Ophthalmologist: ELBW 62%, FT Controls 34%, p<0.0001 Ear/nose/throat: ELBW 14%, FT Controls 6%, p<0.05 Occupational therapist: ELBW 7%, FT Controls 1%, p=0.002 Speech therapist: ELBW 8%, FT Controls 0%, p<0.002 Special Education: ELBW 48%, FT Controls 10%, p<0.0001 Prescription Glasses: ELBW 36%, FT Controls 10%, p<0.001	to generalizability: different era of natural care 2 white race 3 access to universal health care in Canada	

Evidence Table 5A. Studies Evaluating Association of LBW to Speech and Language Disorders
Part III

Author, Year	Associations found	Potential Biases	Comments
Schendel 1997 98033417	Even apparently well VLBW infants with no overt physical impairment are consistently at higher risk for all measures of DELAY than MLBW or NBW infants. VLBW have DELAY in all areas of function with greatest risk for delay in gross motor domain. "Abnormal" – VLBW 10.9%, NBW 2.9%, p = 0.001 Personal-Social =1 delays: VLBW 7.1%, NBW 2.2%, p = 0.001 Language = 1delays: VLBW 8.8%, NBW 4%, p = 0.01 Fine motor-adaptive = 1 delays: VLBW 7.9%, NBW 2.2%, p = 0.001 Gross motor =1 delays: VLBW 10.7%, NBW 1.8%, p = 0.001	The people administering the Denver test were not blinded and were aware of degree of prematurity. The adjusted age at f/u had very wide range 9-34 months	Study was government funded

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Northern Neonatal Nursing Initative Trial Group 1996 96304894	Location: UK Years of Birth: 1990-1992 Mean GA (range), wk: 29 (27-31) Mean BW (range), g: 1253 (965-1543) Male: 39% Race: ND Enrolled: 776 Evaluated: 776 Number of sites: 16	GA <32 weeks; resident in northern UK	ND	Experiment 1: fresh frozen plasma treatment (257) Experiment 2: gelatin plasma substitute (261) Glucose controls (258)	Randomized controlled trial (2 years)
Hack 1996 97066007	Location: US Years of Birth: 7/1982-6/1988, 1/1990-12/1992 Mean GA (range), wk: Sample 1: 25.9±2 (22-31) Sample 1: 25.7±2 (22-31) Mean BW (range), g: Sample 1: 688.6±73 (560-740) Sample 2: 670.6±56 (502-742) Male: Sample 1: 28% Sample 2: 29% Race: White Sample 1: 31% Sample 2: 37% Enrolled: 280 Evaluated: 280 Number of sites: 1	BW 500-759 g Survived to 20 months corrected Age	ND	Sample 1: VLBW survived infants born in 1990-1992 (surfactant/dex era) (114) Sample 2: VLBW survived infants born in 1982-1988 (surfactant and less dex. era) (166)	Prospective cohort (followed to 20 months corrected age)
Hack 2000 20358826	Location: US Years of Birth: : 1/1/1992-2/31/1995 Mean GA (range), wk: 26.4±1.8 Mean BW (range), g: 813±125 Male: 43% Race: ND Enrolled: 333 Evaluated: 221 Number of sites: 1	BW<1000g	Major congenital malformations	VLBW infants (221)	Prospective cohort

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Wood 2000 20373840	Location: UK and Ireland Years of Birth: 1995-1996 Mean GA (range), wk: 22-25 Mean BW (range), g: ND Male: ND Race: ND Enrolled: 314 Evaluated: 283 Number of sites: 276	GA 20-25 weeks survivors	ND	Preterm infants (283)	Prospective cohort (30 [28-40] months)
Singer 1997 98049057 Singer 2001 21163669	Location: US Years of Birth: 1989-1991 Mean GA (range), wk: Sample 1: 27±2 Sample 2: 30±2 Controls: 40±2 Mean BW (range), g: Sample 1: 956±248 Sample 2: 1252±178 Controls: 3451±526 Male: Sample 1: 52% Sample 2: 43% Controls: 50% Race: White Sample 1: 55% Sample 2: 48% Controls: 51% SES: Hollingshed classification: Sample 1: 3.5±1 Sample 2: 3.6±1 Controls: 3.6±1 Enrolled: 464 Evaluated: 206 (123 controls) Number of sites: 3	Cases (sample 1&2): premature infants, BW < 1500g Controls: term infants with no diagnosed medical illness or abnormalities at birth, >36 weeks, GW>2500g	Major congenital abnormality Drug exposure Maternal illness HIV Maternal mental retardation >2 hours driving time from hospital	Sample 1: VLBW infants with BPD infants (122) Sample 2: VLBW without BPD (84) Sample 3: Full term infants (123)	Prospective cohort (followed to 3 years corrected age)

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Schmidt 2001 21298249	Location: Canada, USA, Australia, New Zealand, Hong Kong Years of Birth: 1996-1998 Mean GA: Sample 1: 25.9 ±1.8 Sample 2: 26 ±1.9 Mean BW: Sample 1: 782 ±131 Sample 2: 783 ± 130 Male: 51% Race: Sample 1:White: 69%, black: 13%, Asian: 5%, other: 12% Sample 2: White: 67%, black: 14%, Asian: 7%, other: 12% Enrolled: 2756 Evaluated: 1202 Number of sites: 32	BW: 500-999g 2 hrs old Born in 1 of the 32 participating centers in Canada, USA or Australia. Born during 1/1996-3/1998	Excluded total 981 (not eligible) Unable to administer study drug within 6 hrs of birth , n=469 Structural heart disease Renal disease or both, or strongly suspected (n=24) dysmorphic feature or congenital abnormalities likely to affect life expectancy or neurologic development or to be associated with structural heart disease or renal disease (n=49) Maternal tocolytic therapy with indomethacin or another prostaglandin inhibitor within 72hr before delivery (n=245) Overt clinical bleeding at more than one site (n=8) Platelet count <50.000 (n=25) Hydrops (n=9) Not considered viable (n=171) Unlikely to be available for f/up (n=31)	Sample 1: Indomethacin group [574] Sample 2: Placebo group [569]	Randomized, multicenter, placebo/controlled, double-blind trial [18 mo CA]

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Battin 1998 99002694	Location: British Columbia, Canada Enrollment period: 1991-1993 Mean GA: ND (range: 23-25 wks) Mean BW: ND (Mean BW for the 333 live births during the study period : for GA of 23 wks: 581, for GA of 24 wks: 648, for GA of 25 wks: 764) Male: ND Race: ND Enrolled: 333 (total live births GA: 23-28 wks) Evaluated : 44 (out of 49 of GA 23-25 surviving to NICU discharge) Number of sites: 2	Prospective cohort: Birth at British Children's Hospital and British Womens' Hospital Born during 1991-1993 Extremely low gestational age (ELGA): 23-25 wks Had follow up at 18 mo of age Historical control group: Born at the same institution Born between 1983-1989 GA: 23-25 wks	Cases of therapeutic termination of pregnancies for lethal congenital anomalies Outborns	Prospective cohort of ELGA born during a period when antenatal steroids, surfactant and dexamethasone for BPD had become an accepted treatment [44]	Prospective observational cohort study and a comparative study with an historical control group (18 months)
Vohr 2000 20295211	Location: US Years of Birth: 1/93-12/94 Median GA (range), wk: Mean BW (range), g: ND Male: ND Race: ND Enrolled: ND Evaluated: ND Number of sites: 12	Live born BW 401-1000 g	ND	1151 extremely low birth weight survivors cared for in the 12 participating centers of the National Institute of Child Health and Human Development Neonatal Research Network	Prospective cohort (18-22 months corrected age)

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Piecuch 1997 98012134	Location: US Years of Birth: 1990-1994 Mean GA (range), wk: Sample 1: 24 Sample 2: 25 Sample 3: 26 Mean BW (range), g: Sample 1: 668±91 (450-850) Sample 2: 790±115 (550-1000) Sample 3: 842±158 (505-1260) Male: Sample 1: 50% Sample 2: 73% Sample 3: 50% Race: ND SES: high social risk Sample 1: 89% Sample 2: 43% Sample 3: 68% Enrolled: 94 Evaluated: 86 Number of sites: 1	24, 25 or 26 week GA Non-anomalous Born at University of California, San Francisco	ND (Died after discharge (2) Accidental severe central nervous system insult after discharge (1) Lost to follow-up (5)}	Sample 1: GA 24 weeks (18) Sample 2: GA 25 weeks (30) Sample 3: GA 26 weeks (38)	Prospective cohort (at 12 months, 18 months, 2 ½ years, 4 ½ years. 7-8 years)
Victorian Infant Collaborative study Group, 1997 97466059	Location: Australia Years of Birth: 1979-80, 1985-87, 1991-92 Mean GA (range), wk: ND Mean BW (range), g: ND Male: ND Race: ND Enrolled: 36 Evaluated: 35 Number of sites: 3	ELBW infants, BW 500-999 g born outside the level III perinatal centers in Victoria, Australia survived to age of 2 years	Excluded infants born in 1979-1980 for current review	ELBW infants (36): Sample 1: born in 1985-1987 (19) Sample 2: born in 1991-1992 (16)	Retrospective cohort (2 years)
Ambalavanan 2000 21031370	Location: US Years of Birth: 1/1990 to 12/1994 Mean GA (range), wk: 26±2 Mean BW (range), g: 829±123 Male: 45% Race: African-American 66% Enrolled: 218 Evaluated: 218 Number of sites: 1	ELBW infants, BW <1000 g	ND	ELBW infants (218)	Retrospective cohort (followed to 18 months of age)

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Cheung 1999 99146391	Location: Canada Years of Birth: 1990-1993 Mean GA (range), wk: Sample 1: 25 (22-29) Sample 2: 26 (24-30) Sample 3: 28 (23-32) Mean BW (range), g: Sample 1: 660±56 Sample 2: 873±73 Sample 3: 1127±71 Male: total 57% Race: ND Enrolled: 187 Evaluated: 164 Number of sites: 2	BW<1250 gm GA < 32 weeks Mild or no significant respiratory disease (O_2 < 30%, RR < 70)	Major congenital abnormalities, syndromes Infants with neurologic insult after discharge from NICU.	Sample 1: BW 500-749 g (26) Sample 2: BW 750-999 g (63) Sample 3: BW 1000-1249 g (75)	Prospective cohort (followed to 24 months adjusted age)
Doyle 2001 21326609 Victorian Infant Collaborative study Group, 1997 97290716	Location: Australia Years of Birth: 1991-92 Mean GA (range), wk: 23-27 Mean BW (range), g: ND Male: ND Race: ND Enrolled: 225 Evaluated: 225 (265 controls) Number of sites: 1	Cases: GA 23-27 weeks, survived to 2 and 5 years of age Controls: randomly selected Contemporaneous normal birth weight controls (BW > 2499 g)	ND	Sample 1: Pretem survivors (N= 401) Controls: Randomly selected contemporaneous normal birth weight controls (BW>2499 grams) (N=265)	Prospective cohort (Doyle - 5 years; Victorian – 2 years)

***some subjects were overlapped with 20307288 (stated in text)**
***possibly overlapped with 98026322**

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Corbet 1995 95264244	Location; USA Years of Birth: 1986-1989 Mean GA: Sample 1: 27 ± 2 Sample 2: 27 ± 2 Mean BW: Sample 1: 934 ± 179 Sample 2: 931 ± 191 Males: Sample 1: 50% Sample 2: 50% Race: Sample 1: whites: 41%, blacks: 37%, others: 22% Sample 2: whites: 46%, blacks: 36%, others: 18% Enrolled: 1046 Evaluated: 597 Number of sites: Multicenter	Born alive Qualifying BW (Not specified in this publications) That were intubated and assigned randomly to receive either synthetic surfactant or air placebo as part of their participation in 3 multicenter RCTS. Had follow up at 1 yr of age	ND	Sample 1: Synthetic surfactant: [314] Sample 2: Air placebo [283]	Combination of 3 multicenter, randomized, double blind studies of synthetic surfactant vs air placebo [1 yr]
Gerdes 1995 95264241	Location: US Years of Birth: 3/1989-4/1990 Mean GA (range), wk: Experiment 1: 27.2±1.7 Experiment 2: 27.2±1.8 Mean BW (range), g: Experiment 1: 907±121 Experiment 2: : 911±125 Male: Experiment 1: 55% Experiment 2: 56% Race: Experiment 1: White 55%, Black 37%, Hispanic 4%, Other 5% Experiment 2: White 60%, Black 30%, Hispanic 5%, Other 5% Enrolled: 826 Evaluated: 508 Number of sites: 33	Mothers who were expected to deliver premature infants with BW 700-1100 g	All exclusion prenatal. 1) Proven fetal lung maturity 2) Known malformation or chromosome anomaly 3) Fetal growth retardation 4) Hydrops 5) Purulent amnionitis 6) Maternal heroin addiction 7) Obstetric decision not to support fetus Postnatal exclusions: 1) Major malformation 2) ≥3 minor anomalies 3) Hydrops	Experiment 1: One doses surfactant (244) Experiment 2: Three doses surfactant (264)	Randomized comparison trial (1 year)

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Marlow 2000 20150342	Location: UK Years of Birth: 1990-1994 Mean GA: ND (Median and Range) Sample 1: 28 (26-31) Sample 2: 28 (26-31) Mean BW: ND (Median and range) Sample 1: 960 (600-2914) Sample 2: 1026 (410-2814) Male: ND Race: ND Enrolled : 27 Evaluated: 15 Number of sites: 1	For sensorineural hearing loss (SNHL) group GA: <33 wks Family resident of Greater Bristol area Records at Hearing Assessment Center of Royal Hospital for Sick children. Born during 1990-1994 Diagnosis of SNHL of 50 dB For control group: Matched controls 2:1 to cases Admitted to the same NICUs as cases Matched for sex and GA and next and preceding matching children in the admission books of St Michael's and Sothmead hospitals	ND	Sample 1: SNHL group [15] Sample 2: Control group [30] Matched with cases for sex, GA, admission dates in NICU	Retrospective case control study with a longitudinal component (unclear if retrospective or prospective) (12 mo CA)
Lee 1998 98442293	Location: Canada Years of Birth: 1990-1995 Mean GA: ND Mean BW: Sample 1: 763 ±157 Sample 2: 807±176 Male: ND Race: ND Enrolled: ND (total N not given, data only for enrolled cases with candidemia: N= 29) Evaluated: 50 Assessed for outcome: 35 (14 cases and 21 controls) Number of sites: 2	For cases: Premature with BW<1250 g Admitted in the NICU s of UAH and RAH from 1990-1995 Diagnosis of candidemia: by at least one positive blood culture Diagnosis of candidal meningitis: By isolation of candida in the CSF or >45x10 ^{6} WBCs in the CSF and candidemia. For controls: Premature with BW <1250 g Admitted to the same NICUs during the same period without candidal infection	*Neonates with major congenital anomalies*	Sample 1: Premature infants <1250 with candidemia and/ or candida meningitis (25) Sample 2: Premature neonates with BW <1250 matched with cases for BW, GA, sex and admission dates, without candidal infection (25)	Retrospective longitudinal comparative study with case control design and cases defined based on exposure to candidemia and matched controls (f/up between 37 and 70 mo CA) Average age at assessment: for cases :31 ±19 mo, and for controls: 28 ±20 mo

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
DeReginer 1997 98041177	Location: US Years of Birth: 1987-1991 Mean GA (range), wk: Sample 1: 28.0±1.5 Sample 2: 27.1±1.2 Sample 3: 27.5±1.7 Mean BW (range), g: Sample 1: 1030±140 Sample 2: 1007±122 Sample 3: 1007±140 Male: ND Race: ND Enrolled: 174 Evaluated: 164 Number of sites: 2	BW =1500 g survived until Discharged Able to match to a patient in other two respiratory groups	Presence of independent of chronic lung disease known to adversely affect neurodevelopment, sensory, or growth, i.e. severe intracranial abnormalities, congenital anomalies or viral infections, etc. Unable to match to a patient in other groups Died after discharged (6) Lost to follow-up (4)	Sample 1: No chronic lung disease (58) Sample 2: Mild chronic lung disease (58) Sample 3: Severe chronic lung disease (58)	Retrospective chart review with marched subject group (1 year of adjusted age)
Kurkinen-Raty 1998 98387235 (All+Lung) ***sample from the same big population as 20284814**	Location: Finland Years of Birth: 1990-1996 Mean GA (range), wk: Cases: 28.2 (23.8- 37.2) Controls: 28.4 (22.9-36.9) Mean BW (range), g: Cases: 1138.3±434 Controls: 1272.4±547.2 Male: ND Race: ND Enrolled: 78 (78 controls) Evaluated: 78 (78) Number of sites: 1	Preterm PROM between 17-30 weeks gestation; singleton; delivered > 2 hr after rupture Controls: preterm no PROM; spontaneous preterm delivery matched for GA and year of delivery.	Rupture unconfirmed or transient	Sample 2: Preterm rupture (78) Sample 2: Preterm delivery no rupture (78)	Retrospective cohort
Kurkinen-Raty, 2000 20284814 ***sample from the same big population as 98197235**	Location: Finland Years of Birth: 1990-1997 Mean GA (range), wk: Cases: 30.5±2.1 Controls: 30.4±2.1 Mean BW (range), g: Cases: 1294±469 Controls: 1605±427 Male: ND Race: ND Enrolled: 103 (103 controls) Evaluated: 103 (103) Number of sites: 1	Casarean delivered singleton, GA 24-33 weeks Controls: spontaneous delivered singleton after regular contractions and/or preterm rupture of the membranes no more than 24 hrs before. The mothers were matched one-to-one by gestational age at delivery plus or minus 1 week.	ND	Sample 1: Indicated preterm (i.e., preterm birth 'indicated' for maternal/fetal reasons (103) Sample 2: Spontaneous preterm delivery due to preterm labor (103)	Retrospective cohort

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Predictors	Predictor Measures	Outcomes	Outcome Measures
Northern Neonatal Nursing Initiative Trial Group 1996 96304894	Cardiovascular or Pulmonary Predictors: use of FFP or plasma substitute to expand vascular volume prophylactically	ND	**CNS Outcomes:** Motor delay Cerebral palsy Seizure disorder Post hemorrhagic hydrocephalus **Ophthalmology:** Visual impairment Blindness **Audiology Outcomes:** Hearing disorders Speech **Other outcomes:** Blind, deaf, or unable to walk – combined outcome No severe disability – combined outcome Overall developmental quotient – Griffith's	Motor delay: Griffith's gross motor quotient >350 below mean Griffith's quotient for speech + hearing >350 below mean
Hack 1996 97066007	General: Birth Weight	500-750 gm	**CNS:** Cerebral palsy Motor and cognitive delay **Ophthalmology:** Blindness **Audiology:** Deafness	Neurosensory status BSID: MDI, PDI

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Predictors	Predictor Measures	Outcomes	Outcome Measures
Hack 2000 20358826	General: 1) Birth weight 2)GA 3) SGA/IUGR 4) Antenatal steroids 5) Jaundice CNS: 1) Intracranial/Intraventricular Hemorrhage 2) Periventricular leukomalacia 3) Ventriculomegaly/ ventricular dilation Cardiovascular/Pulmonary: Chronic lung disease Gastrointestinal: Necrotizing "entroclitis" Other: 1) Infectious Disease 2) Dexamethasone 3) Perinatal factors (chorioamnionotis) 4) Multiple birth 5) C-section 6) Social risk 7) Male sex	ND	**CNS:** Cerebral palsy Motor delay Cognitive delay MDI score<70 Post hemorrhagic Hydrocephalus **Ophthalmology**: Blindness **Audiology:** Deafness	Neurologic abnormality - includes: CP, hypotonia, hypertonia Shunt-dependent hydrocephalus

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Predictors	Predictor Measures	Outcomes	Outcome Measures
Wood 2000 20373840	*General:* 1) GA 2) Gender Other: Perinatal Factors→ Multiple gestation	ND	**CNS:** Motor delay Cognitive delay Seizure disorder Overall development **Ophthalmology:** Visual impairment Blindness **Audiology:** Hearing disorder Deafness Speech Communication disorder **Other:** Severely disabled Other disability No disability Disability of hearing, vision, or communication	Bayley scales Severe disability = need of physical assistance to perform daily activities. If disability did not fit into this category = "other disability"
Singer 1997 98049057 Singer 2001 21163669	Cardiovascular or pulmonary predictors: 1) Bronchopulmonary dysplasia General : BW, Neurologic risk Other: Race, Socioeconomic status	BPD: preterm,<1500g BW, oxygen for >28 days with radiographic evidence of CLD	**CNS outcomes:** Cerebral palsy Cognitive delay Mental retardation **Ophthalmology outcomes:** Visual impairment **Audiology outcomes:** Hearing disorders Speech Language Communication disorder	Bayley scale of infant development Language (speech/communication) measured by Battelle Developmental Communication Subscale Domain→ receptive, expressive and total communication scores converted to DQ mean 100 and SD 15.

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Predictors	Predictor Measures	Outcomes	Outcome Measures
Schmidt 2001 21298249	1) Prophylactic indomethacin administration : 0.1 mg/kg Q24 hrs X 3 days (vs NS placebo) in VLBW infants, during first 6 hrs of life	Nor further specified	Primary outcomes at 18 months of age: 1) Composite outcome: death or impairment 2) Death before 18 mo corrected age 3) Cerebral palsy 4) Cognitive delay (MDI<70) 5) Hearing loss requiring amplification 6) Bilateral blindness Secondary long term outcomes outcomes: 1) Hydrocephalus, necessitating the placement of shunt 2) Seizure disorders 3) Microcephaly (HC<3 d %)	1) Death before a corrected age of 18 months or documentation in survivors of one of the following: CP, Cognitive delay, Hearing loss requiring amplification, B/L blindness 2) Cerebral palsy diagnosed if had nonprogressive motor impairment with abnormal muscle tone and decreased range or control of movements. 3) Cognitive delay: as MDI less than 70 (2SD below the mean of 100) on the Bayley scale between 85-114: classified as normal, Scores below 70: marked cognitive delay. 4) Documentation of composite primary outcome: required documentation that the infant had died or had survived with one of the 4 types of impairment. A single missing component of the f/up assessment would result in designation of missing for primary outcome. A priori criteria for definitions of presence or absence of component of the primary outcome. 5) In cases it was difficult to obtain Audiologic test results, deafness requiring amplification was assumed to be absent if no such indication was present during the Bayley test. (n=27) 6) Blindness: a corrected visual Acuity of less than 20/200. F/up evaluation around 18 mo: allowed range 18-21 mo. (Home visits were permitted when necessary)

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Predictors	Predictor Measures	Outcomes	Outcome Measures
Battin 1998 99002694	General: 1) GA (23-25 wks) In comparative component with historical control group General: 1) Birth during a period with routine use of: antenatal steroids, surfactant and dexamethasone for BPD (vs birth in presurfactant, presteroid period)	ND	**CNS:** Neurodevelopmental outcome CP Low MDI (below 2 SDs) **Ophthalmology- Audiology:** Blind, Deaf	Neurologic exam Bayley scale: MDI, PDI Formal hearing test Ophthalmologic examination
Vohr 2000 20295211	**General:** 1) Birth weight 2) Maternal disease (HTN) 3) Antenatal steroids CNS: 1) Intracranial/Intraventricular hemorrhage (GR 3 to $ IVH/PVL) Cardiovascular or Pulmonary: 1) Chronic lung disease (oxygen requirement at 36 weeks) 2) Other: postnatal steroids 3) Other: Surfactant Gastrointestinal: 1) Necrotizing “enterocolitis” Other: 1) Other: male sex 2) Other: Race (white) 3) Other: sepsis (early and late onset) *4)* Other: maternal education	GR 3 to 4 IVH. PVL undefined sepsis undefined	**CNS :** Cerebral palsy **Neurodevelopmental:** Motor delay (sitting, walking, picer grasp, feeding) Seizure disorder Post hemorrhagic Hydrocephalus (PHH) and shunt Other: Neurologic exam (normal; abnormal) Development (MDI and PDI by Bayley II Scale) **Ophthalmology :** Visual impairment (any) Blindness (unilateral, bilateral) **Audiology:** Hearing disorders	“normal Neurologic exam”: no abnormalities on neurologic exams

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Predictors	Predictor Measures	Outcomes	Outcome Measures
Piecuch 1997 98012134	General predictors: 1) GA CNS predictors: 1) intracranial/ intraventricular hemorrhage 2) periventricular leukomalacia *Cardiovascular or pulmonary predictors:* 1) chronic lung disease *Other predictors:* 1) social risk: economic 2) social risk: substance abuse	CLD - at 36 weeks PCA, requirement for supplemental O_2 IVH grade 3 or 4 & PVL, according to sonogram Social risk economic - maternal education <12 grade; complete unemployment in household; or government assistance for health insurance Social risk substance abuse - positive toxicology screens or confirmed history of drug or alcohol abuse	**CNS outcomes:** Cerebral palsy Cognitive delay **Ophthalmology outcomes:** Visual impairment **Audiology outcomes:** Hearing disorders	Visual – Near point tests or Snellen eye charts Audiologic - behavioral testing followed by BAER or pure tone audiometry. Cognitive outcome - Bayley scales at 12 and 18 months; Stanford-Binet at 2.5-4 years; McCarthy scales at 4-6 years. Abnormal neurological outcome – CP, quadriplegia, dysplegia, hemiplegia Suspicious neurological outcome - clumsiness, tremors Severe neurosensory abnormalities – Bilateral hearing loss, blindness Mild neurosensory abnormalities - high frequency hearing loss without hearing aids, visual deficit without glasses
Victorian Infant Collaborative study Group, 1997 97466059 Arch Dis Child	Other: time period of birth	ND	**CNS:** Cerebral Palsy Cognitive delay Post Hemorrhagic Hydrocephalus (PHH) Ophthalmology: Blindness **Audiology**: Deafness **Other:** Sensorineural disability: severe, mental, moderate, none.	CP neurologic exam Bayley MDI, PDI scores Blindness-not stated Deafness-not stated Degrees of sensorineural delay are defined as an aggregate measure and are approximated.
Victorian Infant Collaborative study Group, 1997 98026322	General: BW Other: period of time when born	Each sample were subdivided into BW=500-749 g and BW=750-999 g 1985-1987 vs. 1991-1992	**CNS:** Cerebral palsy Neurodevelopmental: Cognitive and motor delay Disability **Ophthalmology:** Blindness **Audiology:** Deafness or hearing aid	CP was not defined Bayley Scales of Infant Development DQ, using the published mean and SD Disability: “Sever” – bilateral blindness, cerebral palsy with the child unlikely ever to walk, or a DQ score <-3SD; “Moderate” – bilateral sensorineural deafness requiring hearing aids, cerebral palsy in children not walking at 2 but expected to walk, or a DQ score from –3SD to <-2 SD; “Mild” – cerebral palsy but walking at 2 , or a DQ score form –2 SD to <-1 SD.

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Predictors	Predictor Measures	Outcomes	Outcome Measures
Ambalavanan 2000 21031370	General: BW, GA, Antenatal steroids, Apgar score Other: Race, Gender Multiple gestation, Maternal education, Maternal age CNS: Intracranial hemorrhage Periventricular/Ventricular Dilation Bronchopulmonary dysplasia GI: Necrotizing "entrocolitis" Interinal perforation, Chorioamnionitis Multiple gestation Maternal education Maternal age	Extensive list of the 21 predictor variables	**CNS:** Motor delay Cerebral palsy Cognitive delay Mental retardation PHH Neurologic exam Major handicap **Ophthalmology:** Visual impairment Blindness **Audiology:** Hearing disorders Deafness	Bayley scales Major handicap-presence of one or any poor outcome (i.e. CP, deadness, blindness). Mental retardation (MDI or PDI <70), PHH requiring sheet
Cheung 1999 99146391	*General predictors:* 1) BW 2) GA 3) Apgar score *CNS predictors:* 1) intracranial/ intraventricular hemorrhage *Cardiovascular or pulmonary predictors:* 1) days of ventilation 2) days of O_2 use *Other predictors:* 1) frequency of apnea 2) mean desaturation of apnea 3) mean frequency of apnea 4) Blisten index (socioeconomic status)	ND	**CNS outcomes:** Motor delay Cerebral palsy Cognitive delay Mental retardation Seizure disorder Neurodevelopmental disability **Ophthalmology outcomes:** Blindness **Audiology outcomes:** Hearing disorders **Growth outcomes:** Weight > 2 SD below the mean Height > 2 SD below the mean HC > 2 SD below the mean	Bayley scores Stanford-Binet Intelligence Scale Peabody Developmental Motor Scale Neurodevelopmental disability: "children with 1 or more of a) cerebral palsy b) legal blindness c) hearing loss d) convulsive disorder e) cognitive delay

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Predictors	Predictor Measures	Outcomes	Outcome Measures
Doyle 2001 21326609 Victorian Infant Collaborative study Group, 1997 97290716 ***some subjects were overlapped with 20307288 (stated in text)** ***possibly overlapped with 98026322**	*General predictors:* 1) GA 2) SGA/IUGR 3) antenatal steroids 4) gender (female) 5) postnatal age *CNS predictors:* 1) intracranial/ intraventricular hemorrhage 2) periventricular leukomalacia *Cardiovascular or pulmonary predictors:* 1) bronchopulmonary dysplasia *Other predictors:* 1) dexamethasone 2) perinatal factors a) multiple birth b) cesarian section 3) socioeconomic variables i) Asian mother ii) higher SEC iii) no English-speaking at home 4) surgery in primary hospital 5) patient with no adverse events	1) SGA/IUGR - BW ratio <0.8 2) intracranial/ intraventricular hemorrhage - Papille system 3) periventricular leukomalacia - cystic lesions in PVWM dx < discharge 4) bronchopulmonary dysplasia - ROS + O_2 Rx after 28 days age 5) dexamethasone - postnatal steroid use	**CNS:** Motor delay Cerebral palsy Cognitive delay Mental retardation **Ophthalmology outcomes:** Blindness **Audiology outcomes:** Hearing disorders Deafness **Other:** Survival without major disability at 5 years age Survival with major neurosensory disability at 5 years age	1) motor delay, cognitive delay - WPPSI-R and alternative IQ tests 2) cerebral palsy - not walking or walking with difficulty 3) mental retardation - IQ < 2 SD below mean for NBW group

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Predictors	Predictor Measures	Outcomes	Outcome Measures
Corbet 1995 95264244	General: 1) Synthetic surfactant (single dose via ET tube of5 mg/kg vs air placebo)	Not further specified	**Growth:** Growth status at 1 yr: 1) Weight 2) Height, 3) HC and percentiles distribution **Other:** Health status at 1 yr: 1) Surgeries 2) Readmissions to hospital 3) CLD,Medications for CLD 4) Respiratory support on exam day 5) Medications for chronic neurologic disease 6) Asthma, Eczema **CNS:** Neurodevelopmental outcome 1) MDI 2) PDI 3) Impairments: Present absent 4) Severity of impairment 5) Type of impairment (MDI<69, MDI 69-84) 6) CP **Audiology** 1) B/L sensorineural deafness 2) Deafness not requiring amplification **Ophthalmology:** (worst exam and last) 1) B/L blindness 2) Visual defect 3) No ROP, mild/moderate ROP, severe ROP) 4) Treatment for ROP (surgery, cryotherapy)	Assessment at 1 yr of corrected age Not further specified

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Predictors	Predictor Measures	Outcomes	Outcome Measures
Gerdes 1995 95264241	Cardiovascular or Pulmonary: Surfactant use	ND	**CNS:** Cerebral palsy Cognitive delay Mental retardation **Ophthalmology:** Visual impairment, Blindness **Audiology:** Hearing Disorder, Deafness **Pulmonary:** 1) Asthma 2)e/o CLD 3) respiratory support @ 1yr **Growth**: Height, Weight, HC **Other**: hospital re-admissions, h/o surgery	Mental retardation Bayley Scales MDI<69

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Predictors	Predictor Measures	Outcomes	Outcome Measures
Marlow 2000 20150342	**General:** 1) Birth weight 2) Apgar score 3) CRIB scores **CNS:** 1) Maximum bilirubin level 2) Abnormal cerebral US scan **Audiology:** 1) Sensorineural hearing loss **Cardiovascular/Pulomonary:** 1) Duration of intubation, respiratory support, oxygen, pH<7.2, base excess 2) Dopamine 3) Furosemide 4) Indomethacin use **Other:** 5) Netilmicin 6) Vancomycin 7) Positive blood cultures 8) Bilirubin >200 ?mol/l 9) Bilirubin>GA x 10 10) Creatinine >60 mmol/l 11) Netilmicin 12) Vancomycin Combination of the above: 1) Bili.200 + acidosis 2) Bili> 200 + sepsis 3) Bili >200+ netilmicin 4) Bili> 200+ vancomycin 5) Bili>200+ furosemide 6) Peak bil+ acidosis 7) Peak bili+ sepsis 8) Peak bili+ netilmicin 9) Peak bili+ furosemide 10) Creatinine>60+ netilmicin or vancomycin or furosemide 11) Netilmicin+furosemide 12) Vancomycin+ furosemide	Not further specified	In case control component: **Audiology:** 1) Sensorineural hearing loss (SNHL) of 50 dB within 9 months from birth In Longitudinal component: **CNS:** 1) Cerebral palsy at 12 months of age in the 2 groups (SNHL and control group)	Cases of SNHL were identified if the hearing loss had been identified within 3 months of discharge home, (within 9 mo from birth); after excluding cases with conductive hearing loss, possible congenital cause, or had neonatal bacterial meningitis

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Predictors	Predictor Measures	Outcomes	Outcome Measures
Lee 1998 98442293	**General:** 1) Candidemia and/or Candidal meningitis	Diagnosis of Candidemia: by at least one positive Blood Culture Diagnosis of Candidal meningitis: by isolation of Candida in the CSF or >45x10 ^{6} WBCs in the CSF and candidemia.	**CNS:** 1) Neurodevelopmental disabilities (NDDs) 2) Cognitive delay 3) Cerebral palsy **Ophthalmology:** 1) Legal blindness **Audiology:** 1) Hearing loss **Growth:** 1) Growth retardation	1) Bayley Scales of Infant development; MDI, PDI for ages < 24 mo. 2) Stanford-Binet Intelligence Scale and Peabody Development Motor Scales for ages > 24 mo . 3) Scores obtained by psychologists, psychometricians, pediatricians specialized. Neurodevelopmental Disabilities: 1) Cerebral palsy (all types and severity) 2) Legal blindness (corrected VA of the better eye<20/200) 3) Hearing loss (neurosensory hearing loss in the better ear > 30 dB) (done by certified audiologist 4) And/or cognitive delay (MDI>3 SDs below the mean) Growth retardation: Weight, Height, HC > 2 SDs below the mean (Between 3-6 yrs CA)
DeReginer 1997 98041177	Cardiovascular/ Pulmonary: Chronic lung disease	Classification based on the duration of supplemental oxygen requirements. "No CLD" – breathing room air at 28 days "Mild CLD" – requiring supplemental oxygen at 28 days but not at 36 weeks PMA Sever CLD" – reqiring oxygen at 28 days and 36 weeks PMA	**General:** Motor and cognitive delay Cerebral palsy **Opthalmology:** Visual impairment Blindness **Audiology:** Hearing loss Deafness **Growth:** Weight Z score Length Z score Head circumference Z score **Other:** any adverse outcome	Bayley PDI & MDI

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part II

Author, Year UI#	Predictors	Predictor Measures	Outcomes	Outcome Measures
Kurkinen-Raty 1998 98387235 ***sample from the same big population as 20284814**	General : PROM	Diagnose was through clinical assessment or with the use of a PROM-test, which detects insulin growth factor binding protein-1 in the cervico-vaginal secretions, or with the use of a nitrazine test.	**CNS:** Motor delay Cerebral delay **Ophthalmology**: Visual Blindness **Audiology:** Hearing disorders **Pulmonary**: Chronic lung disease **Growth:** weight percent **Other:** Days of re-hospitalization Steroid therapy at followed up	Neurologic exams Diagnosis of CLD was made if infants required oxygen, continuous bronchodilator, or steroid tx because of respiratory signs and symptoms. Diagnoses of RDS were made based on need for respiratory support, radiologic findings, and clinical assessments
Kurkinen-Raty, 2000 20284814 ***sample from the same big population as 98197235**	General predictors: Birth weight GA Antenatal steroids Cord pH Bronchopulmonary dysphasia (BPD) Other predictors: Indicated preterm delivery Spontaneous perterm delivery	BPD diagnoses were based on radiologic finding	**CNS:** Motor delay Cerebral palsy **Ophthalmology** Visual impairment **Audiology** Hearing disorder **Pulmonary** Chronic lung disease (CLD) at 1 year **Growth:** Wt, Ht, HC	Motor delay = abnormalities of tone or reflexes but functionally normal or borderline CP = spastic diplegia or hemiplegia or spastictetraplegia Diagnosis of CLD was made if infants required oxygen, continuous bronchodilator, or steroid tx because of respiratory signs and symptoms.

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part III

Author, Year	Associations found	Potential Biases
Northern Neonatal Nursing Initiative Trial Group 1996 96304894	No significant differences by Griffith's Developmental quotients, incidence of CP, seizures, hearing disorders. Initial demographics available in an earlier study.	Study was government and private funded
Hack 1996 97066007 Pediatrics	MR (MDI<84) CP Blind Deaf Major Neurosensory abnormal +MDI<80 1982-1988 52% 10% 10% - 49% 1990-1992 34% 10% 2% 6% 35% 20-month Neurodevelopmental outcomes did not change appreciably between the 2 eras. 20% of infants had subnormal cognitive function (MDI<70) and 10% had CP during 1990-1992 period. One third of infants with BW 500-750 gram had major neurosensory abnormalities and / or MDI<80.	No data on funding source
Hack 2000 20358826	*MDI Score < 70:* CLD: 55% (49/89); 2.18 (1.20-3.94) *MDI Score<70 (multi stepwise logistic regression)* Male sex: 2.73 (1.52-4.92) Social risk: 1.48 (1.09-2.00) CLD: 2.18 (1.20-3.94) *OR adjusted for sex, social risk & BW:* Gr III-IV IVH: 50% (16/32); 8.55 (3.52-20.76) 50% (8/16); 4.45 (1.54-12.84) 50% (17/34); 5.48 (2.41-12.47) CLD: 30% (27/89); 3.09 (1.51-6.35) Sepsis: 14% (13/93); 3.47 (1.16-10.36) Jaundice: 26% (6/23); 5.15 (1.63-16.22) *Mult. Stepwise Logistic regression:* *Male sex: 2.79 (1.02-7.62)* *Sepsis: 3.15 (1.05-9.48)* *Jaundice: 4.80 (1.46-15.73)* *Predictors of neurologic abnormality were a severely abnormal finding on cerebral ultrasound (OR, 8,09; 95% CI 3.69-17.71) and chronic lung disease (OR 2.46; 95% CI 1.12-5.40); predictors of deafness were male sex (OR 2.79 95% CI 1.02-7.62), sepsis (OR 3.15 95 % CI 1.05-9.48), and jaundice (maximal bilirubin level >171)*	The authors concluded that there is an urgent need for research into the etiology and prevention of neonatal morbidity.

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part III

Author, Year	Associations found	Potential Biases
Wood 2000 20373840	Infants 22-25 weeks GA developmentally assessed at median 30 months • 138/283 had disability 49%(64 met criteria for severe disability) • 49% no disability • 53/283 severely delayed 19%(Bayley below 3 SD) • 32/283 2-3 below SD 11% • 28 severe neuromotor disability 10% • 7 blind or perceived light only 2% • 8 hearing loss that was uncorrectable or required hearing aids 3% Survived without overall disability 22 wks----------0.7 % 23 wks----------5% 24 wks----------12% 25 wks----------23% Severe disability at 30 months 22 ----------0.7% 23 ----------3% 24----------6% 25----------9% • no relation between morbidity pattern and either gestational age &multiple birth • boys were likely to be disabled than girls	Severe disability common; children born extremely premature

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part III

Author, Year	Associations found	Potential Biases
Singer 1997 98049057 Singer 2001 21163669	Evaluation at 36 months corrected age. VLBW, VLBW with BPD, full term (FT). Bayley MDI / % with MDI below 70 VLBW 90 ± 16 (38-126) 11% VLBW w/ BPD 84 ± 24 (10-116) 21% FT 96 ± 12 (57-127) 4% P = 0.001 for VLBW vs. VLBW w/ BPD Bayley PDI / % with PDI below 70 VLBW 98 ± 20 (33-122) 9% VLBW w/ BPD 84 ± 29 (8-127) 9% FT 103 ± 15 (58-128) 1% P = 0.001 for VLBW vs. VLBW w/ BPD At 3 years BPD predicted poorer motor outcome but not poorer mental outcome. **Receptive DQ**: BPD < VLBW < Term, p < 05 **Receptive DQ < 85:** BPD 49%, VLBW 34%, Term 30%, BPD < VLBW + Term p < .05 **Expressive DQ:** BPD < VLBW + Term, p < .05 **Expressive DQ<85:** BPD 44%, VLBW 25%, Term 25% BPD < VLBW + Term p < .05 **Communication DQ**: BPD < VLBW + Term, p < .05 **Communication DQ < 85:** BPD 43%, VLBW 31%, Term 28%, NS Rank order listing of risk factors in order of magnitude of effect and the number of communication DQ lowered by the risk factor: PDA lowered DQ by 13 points, Minority race by 6 points, lower socioeconomic status by 5 points, and higher neurologic risk by 5 points. p .001 **Bayley Scales MDI:** BPD 83.7 ± 24, VLBW 90 ±16, Term 96.4 ± 12, BPD < VLBW < Term, p< 0.05 **Bayley Scales PDI:** BPD 84.1 28, VLBW 97.4 19, Term 102.8 14 BPD < VLBW + Term, p< .05 **ROP:** BPD 43%, VLBW 4%, p= .001 **Seizures**: BPD 7%, **Neurologic score**: BPD 1.3 ± 2, VLBW 58 ± 1, p < .001	Single region, but at least it is a region Unclear if examiners were blinded to groups status Study was government funded

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part III

Author, Year	Associations found	Potential Biases
Schmidt 2001 21298249	1) There was no difference in primary outcomes between the 2 groups at 18 months of age. 2) Among the 574 infants who were assigned to prophylaxis with indomethacin, 271 (47%) died or survived with impairment as compared with 261 of 569 infants (46%) assigned to placebo (OR: 1.1; 95% Confidence intervals; 0.8-1.4) 3) In VLBW infants, prophylaxis with indomethacine does not improve the rate of survival without neurosensory impairments at 18 months of age 4) There was no difference in any of the secondary outcomes between the 2 groups, at 18 months of age. **Primary: Composite / CNS Outcomes:** **Indomethacin vs. Placebo** • Death or impairment 271/574(47%) vs. 261/569 (46%) • Death before 18 mo 121/595 (21%) vs 111/594 (19%) • Cerebral palsy 58/467 (12%) vs 55/477 (12%) • Cognitive delay (MDI<70 by Bayley scale 118 /444 (27%) vs 117/457 (26%) **Audiology outcome:** • Hearing loss requiring amplification 10/456 (2%) vs 10/466 (2%) **Ophthalmology outcome:** • Bilateral blindness 9/456 (2%) vs 7/472 (1%) (Odds ratios adjusted for BW stratum and Center) **Secondary CNS outcomes** were not affected by indomethacin administration: • Hydrocephalus requiring shunt 15/470 (3%) vs 9/480 (2%) • Seizure disorder 8/470 (2%) vs 7/483 (1%) • Microcephaly 49/461 (11%) v s 54/475 (11%) Kaplan Meier estimates of survival in the 2 groups: • 0 months n=601 vs 601 • 6 months n=479 (80%) vs 490 (82%) • 12 months n=473 (79%) vs 487 (81%) • 18 months n=470 (78%) vs 483 (80%)	1) By using the Bayley test at 18 mo the authors found that more than one quarter of all surviving infants had moderate to severe cognitive delays, defined by MDIs< 70. The validity of the MDI score at this age as a predictor of later intellectual functioning remains to be determined. 2) At a post hoc calculation the study had a 90% power to detect a 20% reduction in risk, had it existed 3) Authors report that the outcome assessments were done blindly by investigators unaware of treatment groups assignments 4) Authors report that they had almost complete ascertainment for the primary outcome at 2 yrs of age.

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part III

Author, Year	Associations found	Potential Biases
Battin 1998 99002694	**CNS outcomes:** Major impairment was present in 36% of infants born at 23-25 wks GA, during 1991-1993 (N=44) 1) Cerebral palsy 9/44 (20%) 2) Low MDI 8/44 (18%) **Ophthalmology** outcome: 1) Blind 4/44 (9%) **Audiology** outcome: 1) Deaf 4/44 (9%) **Combined** outcome: 1) Overall impaired 16/44 (36%) 2) Multiple handicaps 6/16 (38%) Analysis of only 24-25 wks GA infants (N=43): Major handicaps: 15/44 (34%) The percentage of infants with major impairments and/ or multiple handicaps, for the 23-25 wks GA group, was the same in 1991-1993 and 1983-1989 periods (However, no data on the number of infants from this cohort that were actually followed up at 18 mo of age)	1) During 1991-93 period there is no concurrent control group for the comparative assessment of neurodevelopmental outcome 2) Group of infants of 23-25 wks GA, born during 1991-1993, was not matched to the historical control group born during 1983-1989. Possibility of confounders cannot be excluded. 3) No data were given on the number of infants in the historical control group that had f/up at 18 mo of age. No data on source of funding
Vohr 2000 20295211	Studied effect of early IVH at 5 to 11 hours of age on IQ distribution and presence of cerebral palsy (CP). Assessed at 36 months CA. N: Early IVH present 29; Early IVH absent 249 Binet IQ: 78.7 (25) vs 87.5 (20); P value 0.09 Binet IQ < 70: 38% vs 19%; P value 0.03 PPVT-R: 76.6 (28) vs 86.0 (21); P value 0.15 CP at 36 months: 25% vs 8%; P value 0.01 Later IVH had effect on Binet IQ similar to early IVH.	IVH rates seems high No data on funding source

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part III

Author, Year	Associations found	Potential Biases
Piecuch 1997 98012134	Mean age at follow-up was 32 months. Bayley exams were done at 18 months. Neurologic abnormalities and CP did not differ significantly across the gestational ages of 24 to 26 weeks. Between 67% and 89% were normal in each gestational age group. Significant differences (P = 0.036) related to gestational age were found in 18 month Bayley exam scores when group as normal borderline or deficient Normal / Deficient 24 wk 28% 39% 25 wk 47% 30% 26 wk 71% 11% Significant differences (P = 0.008) related to gestational age were found in the combined end point of CP or an abnormal Bayley exam score: Neither / One / Both 24 wk 28% 39% 33% 25 wk 47% 23% 30% 26 wk 63% 34% 3%	All inborn infants No data on funding source
Victorian Infant Collaborative study Group, 1997 97466059	*All children born outside the level III perinatal centers. Assessment at 2 years corrected age.* *1985-1987* / *1991-1992* *n* 19 16 *Cerebral Palsy* 19.1% 12.5% *Cognitive delay* 19.1% 18.8% *Blind* 5.6% 6.2% *Deaf* 0 0 *Sensorineural disability* *Mild* 15.8% 6.2% *Moderate* 0 0 Severe 5.3% 12.5%	Incomplete reporting of demographic data, methods and results. Study was government funded

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part III

Author, Year	Associations found	Potential Biases
Victorian Infant Collaborative study Group, 1997 98026322	Birth weight < 1000g; assessed at 2 years corrected age. Cohort n DQ < -3 SD DQ –3 to –2 SD DQ –2 to –1 SD DQ> -1 SD '91-'92 237 5.9% 6.3% 13.9% 73.4% '85-'87 211 6.2% 4.3% 14.2% 75.4% Cohort n Mild CP Mod. CP Severe CP Any CP Blindness Deaf '91-'92 237 3.8% 1.7% 3.8% 9.3% 2.1% 0.8% '85-'87 211 NS NS NS 6.6% 4.3% 0.5% Cohort No disability Mild Disability Moderate disability Severe disability '91-92 n = 237 71.3% 14.8% 7.2% 6.8% '85-'87 n = 211 71.6% 15.6% 6.2% 6.6%	Incomplete reporting of demographic data, methods and results. Study was government funded

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part III

Author, Year	Associations found	Potential Biases
Ambalavanan 2000 21031370	ELBW: MDI<68 : 12% PDI<68: 20% Major handicap: 28% CP:28% MR 16% Post-hemorrhagic hydrocephalus: 5% Deaf 1.4% Blindness 1% Predictors of major handicap (Low MDI and/or PDI): Grade of IVH, PVL, absence of chorio (in this population, not in most others), NEC≥II; race; multiple gestation, BPD, maternal education For ELBW infants without IVH, the prevalence of major handicap, low MDI, and Low PDI was 25%, 17%, 16%, respectively. For ELBW infants with grade III IVH, the prevalence of major handicap, low MDI, and Low PDI was 33%, 29%, 24% respectively. For ELBW infants with grade IV IVH, the prevalence of major handicap, low MDI, and Low PDI was 69%, 44%, 63% respectively. This study identifies major determinants of adverse neurodevelopmental outcome (i.e. major handicaps, low MDI, low PDI) of ELBW (<1 kg) infants born 1990-1994. Grade of IVH is strong predictor of adverse outcome. But note large % of ELBW without IVH who had major handicap, low MDI, and Low PDI. **BPD** was a significant determinant of low MDI and PDI. Mat education level was significant determinant of neurodevelopmental outcome. NEC, race, multiple gestation, PVL independently contributed to poor outcome in ELBW infant. Lower BW predicted low PDI.	Retrospective, relatively small sample size (218). No data on funding source
Cheung 1999 99146391	Mental score: *Days of ventilation: (N=64) <0.0001* Motor Score: *Days of ventilation: (N=164) <0.004* Mental Score: *Grade of IVH: (N=164) 0.003* Motor Score: *Grade of IVH: (N=164) <0.0001* Mental Score*:* *Infants <1250g with gr. 3 or 4 IVH: (N=50) <0.001* Motor Score*:* *Infants <1250g with gr. 3 or 4 IVH: (N=50) <0.001*	No data on funding source

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part III

Author, Year	Associations found	Potential Biases
Doyle 2001 21326609 Victorian Infant Collaborative study Group, 1997 97290716 ***some subjects were overlapped with 20307288 (stated in text) *possibly overlapped with 98026322**	Evaluation at 5 years corrected age: **CP :** 23-27 wk survivors (11.3%) 25/221 Blindness : 23-27 wk (1.8%) 4/221 FT controls (0%) FT control 0% **Deafness : 23-27 wk (0.9%) 2/221** FT control 0% **IQ <-2 SD: 23-27 wk (15.4%) 34/221** **Major neurosensory disability** 23 –27 wk (19.6%) 44/225 FT control (4.1%) 10/245 **Major disability among survivors** 23 wk GA: 2/5 (40%) 24 wk GA: 7/21 (33%) 25 wk GA: 13/51 (25%) 26 wk GA: 17/71 (24%) 27 wk GA: 5/79 (6%) Overall 23-27 wk: 19% **OR for survival with major disability at 5 years:** OR each 1 wk increase in GA = 0.59 (95% CI 0.43, 0.8) **Prognostic factors with major disability at 5 years:** IVH, cystic PVL, surgery during primary hospitalization, postnatal steroid treatment. Rates of survival free of major disability for surviving PT infants: None 96/103 =93% One 59/71 =83 % Two 23/43 =53 % Three 3/9 =33% Four 0/1 = 0 Evaluation at 2 years corrected age. Data shown are for births in 1991-1992. Gestational age Sensorineural disability (% of survivors) n Severe Moderate Mild None 23 weeks 5 29% 20% 40% 20% 24 weeks 21 14.3% 19% 33.3% 33.3% 25 weeks 51 5.9% 21.6% 25% 47% 26 weeks 68 8.8% 11.8% 20.6% 58.8% 27 weeks 74 1.4% 10.8% 23% 64.9% Overall 219 6.4% 14.6% 24.2% 54.8% Decrease in disability with increase in gestational age was significant, p = 0.014. Also showed significant fall in severe disability with increase in gestational age, Odds ratio = 0.58 (0.36-0.94) Comparison of cohorts born in 1985-1987 vs. 1991: 1992 did not demonstrate any difference between cohorts.	Perinatal data lacking on some infants, Especially outborn (in level II or I) Different methods of testing IQ Different times of assessing Neurodevelopmental outcome Some children not evaluated at 5 years (evaluated at 2 years) 210/401 preterm infants were assessed at both 2 and 5 years The classification of disability or no disability was the same at both 2 and 5 years (90.5% agreement; k=0.691) Inadequate discussion of study population demographics Also various surrogate data Study was government funded

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part III

Author, Year	Associations found	Potential Biases
Corbet 1995 95264244	**Growth** AT 1 YR: Mean measurements of Height (74 cm), weight (9.1 kg) and HC (46 cm) and growth percentiles were equivalent in the 2 groups. **Health Status** AT 1 YR: No difference in parameters between 2 groups 1) Surgeries (33% vs 34%) 2) Readmission to hospital (45% vs 39%) 2) CLD (11% vs 10%) 4) Medications for CLD (14% vs 14%) 3) Respiratory support (4% vs 2%) 4) Med. for chronic neurologic problems (1% vs 2%) 5) Asthma (this only was s/s : 9% vs 3%) 8) Eczema (2% vs 1%) **Neurodevelopmental Outcome:** No difference in the outcomes between the 2 groups in these parameters. 1) Mean MDI (values <50= 49): 2) Mean MDI (only children with MDI>69) 2) Number of children with MDI<69: 4) Number of children with PDI<69 3) Mean PDI (values<50=49) 6) Mean PDI (only children with PDI>69) **CNS Impairment:** No difference in any impairments between 2 groups 1) Present: 43% vs 37% 2) Absent: 57% vs 63% 2) Mild/moderate: 20% vs 14% 4) Severe:23% vs 23% 3) MDI<69: 17% vs 16% 6) MDI: 69-84: 18% vs 14% 4) CP mild: 8% vs 7% 8) CP moderate/severe: 7% vs 7% **Audiology:** 1) B/L sensorineural hearing deafness: 0% vs 1% 2) Deafness not needing amplification: 0% vs 1% **Ophthalmology:** 1) B/L blindness: 3% vs 2% 2) Visual defect: 8% vs 8% Worst examination 2) No ROP: 30% vs 33% 2) Mild/moderate ROP: 53% vs 52% 3) Severe ROP: 17% vs 15% 4) Surgical treatment for ROP:10% vs 12% 4) Cryotherapy for ROP: 5% vs 6% Last examination 5) No ROP: 69% vs 72% 2) Mild/moderate ROP: 26% vs 22% 6) Severe ROP: 5% vs 6% 4) Surgical treatment for ROP: 4% vs 4% 7) Cryotherapy for ROP: 2% vs 3% Infants who survived after treatment at birth with single dose synthetic surfactant fare as well in terms of growth, development and late morbidities as infants who survive without treatment. No difference in medical history during first year of life, growth, incidence of visual or auditory defects, CP, neurodevelopmental delay at 1 yr adjusted age.	The incidence of severe impairment in the 19% of infants who did not return for evaluation at the age of 1 yr may be higher than in those who were evaluated. Source of funding not reported. The neurodevelopmental evaluation of infants at 1 yr may not be absolutely reliable for the estimation of later outcome. The estimated mental retardation is likely to be low, and the estimated CP is likely to be high, compared to estimates at 2 and 3 yrs.

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part III

Author, Year	Associations found	Potential Biases
Gerdes 1995 95264241	Severe ROP: 1 dose: 47(16) 3 dose: 35(11) Physical evidence of CLD: 1 dose: 43(18) 3 dose: 40(15) Medication for CLD: 1 dose: 35(14) 3 dose: 30(11) Medication for chronic neurologic disease: 1 dose: 12(5) 3 dose: 3(1) Index<2 SD (%): 1 dose: 29(15) 3 dose: 30(13) Impairment present: 1 dose: 106(44) 3 dose: 92(35) No impairment: 1 dose: 123(51) 3 dose: 155(59) Severity of impairment: Mild/moderate: 1 dose: 40(17) 3 dose: 39(15) Serious: 1 dose: 66(27) 3 dose: 53(20) Types of impairments: MDI<69: 1 dose: 40(16) 3 dose: 38(14) Moderate/severe CP: 1 dose: 22(9) 3 dose: 16(6) Bilateral sensorineural deafness: 1 dose: 5(2) 3 dose: 10(2) Deafness not requiring amplification: 1 dose: 5(2) 3 dose: 2(1) Bilateral blindness: 1 dose: 10(4) 3 dose: 4(2) Visual defect: 1 dose: 24(10) 3 dose: 22(8)	25% loss to follow up, equal in both groups; 1 year follow-up does not predict long-term outcome from all infants No data on funding source "Prenatal and postantal exclusion criteria were identical to those used in an earlier prophylactic trial of this synthetic surfactant" Died by 1-year adjusted age Lost to follow-up

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part III

Author, Year	Associations found	Potential Biases
Marlow 2000 20150342	Pulmonary and Other predictors evaluation for **Audiology outcome**. Children with sensorineural hearing loss [15] as compared to control group[30] had longer periods of: 1) Intubation, (14 ds vs 2 ds) 2) Ventilation (34 ds vs 6 ds) 3) Oxygen therapy (57 ds vs 10 ds) 4) Acidosis (12 ds vs 0.5 ds), and 5) More treatments with dopamine (33% vs 7%)or 6) Furosemide (87% vs 53%) 7) Neither P/T of aminoglycosides 8) nor duration of jaundice 9) or level of bilirubin varied between the 2 groups. SNHL was more likely when : 1) netilmicin use coexisted with the peak of bilirubin (87% vs 14%)_ 2) when acidosis occurred when bilirubin was over 200 ?mol/l, (31% vs 4%) 3) when furosemide was used in the face of high creatinine levels (64% vs 27%) 4) when furosemide was used with netilmicin (67% vs 37%) **CNS outcome at 12 mo:** At 12 months of age evidence of cerebral palsy was present in 7/15 (47%) of children with SNHL vs 2/30 (7%) of children without SNHL.(p=0.022)	1) Very small sample size (cases with SNHL only 15) 2) Analyzed too many predictors and combination thereof, for very few outcomes. Very wide confidence intervals; and even those predictors found to be associated with the SNHL this may have been due to chance. 3) The association found between SNHL and cerebral palsy was <u>not</u> based on an adjusted analyses for possible confounders; 4) The 2 groups were different in many factors that were associated with both SNHL and CP Not reported source of funding

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part III

Author, Year	Associations found			Potential Biases
Lee 1998 98442293	**Growth, CNS and Audiology, and ophthalmology outcomes** for prematures<1250 g with candidemia/candida meningitis	Cases	Controls	Cannot exclude missed association due to the small number of patients analyzed n both groups
	Growth:			
	1) No difference in Growth retardation:	7/14 survivors(50%)	11/21 survivors (50%)	
	CNS:			
	1) No difference in MDIs of survivors	83 ±20	90 ±20 (p>0.05)	
	2) Lower PDIs in survivors	71 ±21	87±18 (p<0.05)	
	3) No difference in overall Neurodevelopmental disabilities (NDDs)	4/14 (29%)	3/21 (14%) (p>0.05)	
	4) Cerebral palsy	4/14 (29%)	3/21 (14%)	
	Ophthalmology:			
	1) Vision loss	2/14 (14%)	1/21 (5%)	
	Audiology:			
	1) Hearing loss	2/14 (14%)	1/21 (5%)	
	(All the children with NDDs had Cerebral palsy with or without visual or hearing deficit)			
	Prematures<1250 g with candidemia/candida meningitis had: Higher Combined mortality and NDDs	60% (OR=3.9; 1.2-12.6)	28% (p< 0.05)	

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part III

Author, Year	Associations found	Potential Biases
DeReginer 1997 98041177	***Chronic lung disease*** *Any adverse outcome:* 2/54 12/54 P<0.001 18/56 *Sensorineural hearing loss:* 0/54 0/54 P<0.05 *3/56* *Low MDI<2 SD from mean:* 0/54 4/54 P<0.05 *5/56* *Low PDI<2 SD from mean:* 1/54 4/54 P<0.05 *7/56* *Weight Z-score:* *No numbers given <0.05* *Chronic lung disease and cerebral palsy, unilateral blindness, length Z-score, head circumference Z-score are not significant.*	Matching scheme used is likely to be ineffective Large proportion of study population excluded by their matching strategy: subjects excluded were: 329/387=85% with no chronic lung disease; 53/111=47.7% with mild chronic lung disease; 122/180=68% with severe chronic lung disease No data on funding source
Kurkinen-Raty 1998 98387235 ***sample from the same big population as 20284814**	Retrospective controlled cohort study of early PROM between 17 and 30 weeks of gestation. Assements at one year corrected age. N = 55 for early PROM and 56 for control. Outcome / Early PROM / Control / OR (CI) Cerebral palsy 18% 16% 1.2 (0.4, 3.1) Delayed motor Development 9% 16% 0.5 (0.2, 1.7) Visual disability 4% 4% 1.0 (0.1, 7.5) Hearing loss 7% 9% 0.8 (0.2, 3.2) Good nuerosensory development 67% 61% 1.2 (0.6, 2.2) Early PROM seems to be a major obstetric and neonatal problem with pulmonary ramifications extending beyond the neonatal period. However, most of these infants can be saved.	No data on funding source

Evidence Table 5B. Studies Evaluating Association of LBW to Audiology Outcomes
Part III

Author, Year	Associations found	Potential Biases
Kurkinen-Raty, 2000 20284814 ***sample from the same big population as 98197235**	**CLD at 1 year age:** Indicated PT delivery: (81) 12/81 (15%) Spontaneous PT delivery: (94) 3/94 (3%) RR 4.6 (1.4, 1.6) **Growth:** Indicated PT delivery: (81) Spontaneous PT delivery: (94) Weight RR =0.03 (-5.3, 0.3) L RR = 0.002 HC RR = 0.03 **CP:** Indicated PT delivery: (81) 5/81 (6%) Spontaneous PT delivery: (94) 10/94 (11%) RR=0.6 (0.25-1.6) **Delayed motor:** Indicated PT delivery: (81) 8/81 (6%) Spontaneous PT delivery: (94) 8/94 (9%) RR 1.2 (0.5-3.0) **Visual disability:** Indicated PT delivery: (81) Spontaneous PT delivery: (94) RR =1.9 (0.5, 7.8) **Hearing loss:** Indicated PT delivery: (81) Spontaneous PT delivery: (94) RR =1.9 (0.5, 7.8) 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 yr age. More infants in 'indicated' group were SGA and were significantly smaller than control group at 1 yr in Wt, HT, and HC. There was no difference between groups in neurosensory outcomes.	Outcome not well defined Difficult to know if lack of difference between groups is due to sample size or event rate. No data on funding source

Evidence Table 6A. Studies Evaluating Association of LBW to Behavioral Disorders
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Nadeau 2001 21163667	Location: Canada Years of Birth: 1987-1990 Median GA (range), wk: Cases: 27.4±1.1 Control: 39.8±1.6 Median BW (range), g: Cases: 1024.3±204.2 Control: 3453.4±497.8 Male: Cases: 51% Control: 50% Race: ND Enrolled: 129 Evaluated: 86 ? 61 (50 controls) Number of sites: 1	Cases: GA<29 weeks, BW<1500 g Controls: Normal BW children , born at the same hospital during the same time period	Cases: Lost to follow-up at 5 years 9 months: families had moved away (33), parents' refusal (10) Lost to follow-up at age 7: families had moved away (10), parents' or school's refusal (13)	Cases: EP/VLBW infants (86? 61)	Prospective cohort (at 18 months, 5 years 9 months, and age 7)
Robson 1997 9055145	Location: Canada Years of Birth: ND Mean GA (range), wk: 32.6±3.4 Mean BW (range), g: 1758.7±521.7 Male: 36% Race: ND Enrolled: 132 Evaluated: 85 Number of sites: 2	LBW cohort: ≤ 2500 g Admitted to neonatal intensive care units at 2 hospitals in a mid-sized Canadian city. English-speaking mothers. Families lived within 100 km of either hospital. Assessments at 7 mos and 12 mos of age.	Significant visual or motor impairments or any other gross neurological or physical anomalies.	Cases: 85 LBW infants No control group	Prospective single-arm cohort study

Evidence Table 6A. Studies Evaluating Association of LBW to Behavioral Disorders
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Breslau 1996 8836807	Location: US Years of Birth: 1983-1985 Mean GA (range), wk: ND Mean BW (range), g: Urban LBW: 14.7%<1500 g, 21.4% 1501-2000 g, 63.9% 2001-2500 g. Suburban LBW: 17.4%<1500 g, 17.9% 1501-2000 g, 64.7% 2001-2500 g. Urban NBW: ND Suburban NBW: ND Male: Urban LBW: 42% Suburban LBW: 52% Urban NBW: 48% Suburban NBW: 54% Race (% African-American): Urban LBW: 80% Suburban LBW: 11% Urban NBW: 48% Suburban NBW: 3% Enrolled: 1095 Evaluated: 823 Urban LBW: 238 Suburban LBW: 235 Urban NBW: 176 Suburban NBW: 174 Number of sites: 2	LBW cohort: ≤ 2500 g NBW cohort: > 2500 g Born between 1983-85, 6- 7 yrs old during 1990-92 when the fieldwork took place. From 2 major hospitals in southeast Michigan: one urban and one suburban. (In each hospital, random samples of LBW and NBW children were drawn).	From the target sample: Children with severe neurologic impairment: severe mental retardation, severe cerebral palsy, blindness.	At 6 yrs (823): Cases: LBW 473: Urban LBW (238) Suburban LBW (235) Controls: NBW 350: Urban NBW (176) Suburban NBW (174)	Nonrandomized comparison study (6 years)

Evidence Table 6A. Studies Evaluating Association of LBW to Behavioral Disorders
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Breslau 2000 20298367	Location: US Years of Birth: 1983-1985 Mean GA (range), wk: ND Mean BW (range), g: ND Male: ND Race (% African-American): Urban LBW: 80% Suburban LBW: 11% Urban NBW: 74% Suburban NBW: 3% Enrolled: 1095 Evaluated: 823→717 Number of sites: ND	LBW cohort: ≤ 2500 g NBW cohort: > 2500 g Born between 1983-85, 6- 7 yrs old during 1990-92; when the initial assessment took place. Follow-up assessment at age 11 (1995-1997). From 2 major hospitals in southeast Michigan: one urban and one suburban. (in each hospital, random samples of LBW and NBW children were drawn).	From the target sample: Children with severe neurologic impairment: severe mental retardation, severe cerebral palsy, blindness.	At 11 yrs (717): Cases: LBW 411: Urban LBW (217) Suburban LBW (194) Controls: NBW 306: Urban NBW (164) Suburban NBW (142)	Nonrandomized comparison study (11 years)

Evidence Table 6A. Studies Evaluating Association of LBW to Behavioral Disorders
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Hille 2001 21319264	Location: US, Canada, Germany, Netherlands Years of Birth: US: 1984-1987 Canada: 1977-1982 Germany: 1985-1986 Netherlands: 1983 Mean GA (range), wk: US: 27±2.3 Canada: 27±2.3 Germany: 29±2.0 Netherlands: 29±2.3 Mean BW (range), g: US: 853±114 Canada: 834±126 Germany: 888±101 Netherlands: 882±105 Male: US: 40% Canada: 45% Germany: 45% Netherlands: 42% Race: White 93% Enrolled: 523 Evaluated: 408 Number of sites: 1	Survivors from 4 population based cohorts of ELBW infants in 4 countries: US – the neonatal brain-hemorrhage cohort (NBH): BW<2000 g Canada – McMaster ELBW cohort (McM): BW<1000 g Germany – Bavarian longitudinal study of children at biological risk (BLS): BW<1500 g and GA<32 weeks Netherlands – the project on preterm and small for gestational age infants (POPS): BW<1500 g and GA<32 weeks	No assessments of CBCL at age 8-19	Cases: ELBW infants from 4 population based cohorts in 4 countries (108): USA (80) Canada (150) Germany (78) Netherlands (100) Controls/Normative Samples: USA had 1200 4 – 11 year old normative controls. Netherlands had 1172 11 year old normative controls. Canada had 145 full-term controls Germany had 335 full-term controls.	Prospective single-arm cohort study

Evidence Table 6A. Studies Evaluating Association of LBW to Behavioral Disorders
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Katz 1996 97145056	Location: UK Years of Birth: 5/83- 4/85 Median GA (range), wk: 29.2±2.5 (26-34) Mean BW (range), g: 1227.5±341.4 (740-2240) Male: Cases: 52% Controls: 55% Race: Cases: 75% White, 19% Black, 6% Asian Controls: 75% White, 12.5% Black, 12.5% Asian Enrolled: 212 Evaluated: 64 (40 controls) Number of sites: 2	≤34 weeks, no major congenital anomaly, 3 cranial u/s in first week of life	Lost to follow-up Too impair due to multiple cognitive, sensory, or motor disabilities, to complete testing	Cases: Preterm infants (64) Controls: Full-term comparison sample (40)	Prospective cohort (6-8 years)
Sajaniemi 1998 99041674	Location: Finland Years of Birth: 1989-1991 Mean GA: Sample 1: 28.9 (23-35) Sample 2: 39.4 (36-43) Mean BW: Sample 1: 1205 (560-2360) Sample 2: 3461 (2510-5360) Male: ND Race: ND Enrolled: ND Evaluated : 160 Number of sites: 1	For Preterm Group (sample 1): GA: 23-34 wks Mother referred to University Central Hospital of Helsinki for threatened preterm delivery Born between 1989-1991 For Full term group (Sample 2): Born in Metropolitan Helsinki Visiting pediatric services in Helsinki for acute infectious diseases	For Preterm group If mothers had chorioamnionitis If mother had insulin dependent diabetes Children with congenital anomalies, by U/S For Full term group Chronic diseases Developmental delay	Sample 1: Preterm infants (80) Sample 2 Full term enrolled at: 20-28 mo of age (80)	Retrospective comparative study (24 mo CA)

Evidence Table 6A. Studies Evaluating Association of LBW to Behavioral Disorders
Part II

Author, Year UI#	Predictors	Predictor Measures	Outcomes	Outcome Measures
Nadeau 2001 21163667	General: GA Other: Family adversity Index	Evaluated at 5 years 9 months, was developed using SES data such as the family status (two-parent, single-parent, blended), age of each parent, their respective levels of education, and professional occupations. 0=low ~ 7=high	**CNS:** Neurodevelopmental: Motor function Cognitive delay Behavioral disorders **Behavior**	Neuromotor development index: Huttenlocher neurological task test McCarthy Scales of Children's Abilities Behaviors wre assessed by peers, teachers, and parents: RCP, TRF, parent's CBCL
Robson 1997 9055145	Developmental status Quality of home environment Early Medical risk Infant temperament	Development measured by The Bayley Scales of Infant Development Quality of Home environment at 7 and 12 mos of age: The HOME Inventory, paternal education, The Blishen Index, preschool version of the HOME Inventory in early childhood Early Medial Risk measured by the Morbidity Scale Infant Temperament and Development: The Carey Infant Temperament Questionnaire when the infants are 7 months of age corrected for prematurity.	Behavior at 5.5 years of age: Inattention Impulsivity	McCarthy Scales of Children's Abilities by the examiner Parental report from the Child Behavior Checklist Task performance test, vigilance tasks Matching Familiar Figures Test
Breslau 1996 8836807	General: 1) LBW (vs Normal BW= NBW) 2) Urban (vs suburban setting) 3) Maternal smoking during pregnancy	BW <2500g Racial composition, whether mothers completed high school, marital status, maternal smoking during pregnancy, maternal substance abuse/dependence during pregnancy.	ADHD (attention deficit hyperactivity disorder) Separation anxiety disorder Simple phobia Overanxious disorder Oppositional defiant disorder	The National Institute of Mental Health Diagnostic Interview Schedule for Children-Parent Teacher Report Form

Evidence Table 6A. Studies Evaluating Association of LBW to Behavioral Disorders
Part II

Author, Year UI#	Predictors	Predictor Measures	Outcomes	Outcome Measures
Breslau 2000 20298367	General: 4) LBW (vs Normal BW= NBW) 5) Urban (vs suburban setting) 6) Maternal smoking during pregnancy	BW <2500g Racial composition, whether mothers completed high school, marital status, maternal smoking during pregnancy, maternal substance abuse/dependence during pregnancy.	Behavior assessment at 11 yrs of age. (Assessment at 6 yrs: reported in 1996 publication) 1) Behavioral problems in 3 domains: Attention, Externalizing behaviors, Internalizing behaviors 2) Severe attention problems (above a cutoff point of 67)	Mother's rating was done with: Child Behavior Checklist (CBCL) Teacher's rating was done with Teacher Report Form (TRF) (teachers were blind to the BW information of the child) Assessments at 11 yrs were conducted blindly to the results of assessments at 6 yrs (reported in another publication) 1) Attention problem subscale; 20 items 2) Externalization problem subscale: 2 subclasses 3) Internalization problem subscale: 3 subclasses
Hille 2001 21319264	Birth weight	ND	Behavior Attention	CBCL – Parents: Total problem score Internalizing behavior (anxious, Socratic), Externalizing behavior (aggressive and delinquent), Social, thought, attention problems
Katz 1996 97145056	General: GA CNS: 1) Intracranial/ Intraventicular hemorrhage 2) Periventricular leukomalacia (cystic PVD) 3) PVD (if unilateral or bilateral periventicular echogenic lesions present on at least 3 scans)	IA IVH: no lesion= consistently NC scans. Mild lesion = germinal hem or small IVH or PVD or mild vent dilation without hem. Severe lesion: blood distends the vents or in parenchyma, or multicystic PVC.	**CNS:** Neurodevelopmental: Attention IQ	Measured by CPT test (Continuous Performance Test), measuring errors of omission or commission. Is also measured by CBCC (Child Behavior Check List): parents check off behavior related to attention and hyperactivity. Measured by British Abilities Scale

Evidence Table 6A. Studies Evaluating Association of LBW to Behavioral Disorders
Part II

Author, Year UI#	Predictors	Predictor Measures	Outcomes	Outcome Measures
Sajaniemi 1998 99041674	General: 1) Prematurity per se 2) Premature with BW< 1000 g vs premature with BW > 1000 g 3) Preeclampsia 4) SGA 5) Duration of NICU stay **CNS:** 1) PVL 2) IVH **Pulmonary:** 1) Duration of ventilation	Not further specified	**CNS:** Neurologic outcome Developmental outcome Temperament profile Behavioral profile	Neurologic outcome: 1) Cerebral palsy 2) Free of major disabilities Developmental outcome: 1) Bayley Scales of Infant Development 2) Mental Development Index (MDI) Temperament: Toddler Temperament questionnaire (TTQ) (contains 97 statements) 9 temperament dimensions: 1) Activity 2) Rhythmicity 3) Approach 4) Adaptability 5) Intensity 6) Mood Persistence 7) Distractability 8) Threshold Behavior: Infant Behavior Record: 1) Social responsiveness 2) Attention 3) Affect 4) Energy level 5) Goal directedness during the test (24 mo CA)

Evidence Table 6A. Studies Evaluating Association of LBW to Behavioral Disorders
Part III

Author, Year	Associations found	Potential Biases
Nadeau 2001 21163667	EP/ VLBW, n = 61 and controls, n = 44. EP/ VLBW: Normal neuromotor function 67%; Abnormal neuromotor function 33%; McCarthy IQ [mean (SD)] 100.3 (19.1) Control: 97%; 3%; 112.8 (16.2) Significance: NS; P < 0.01 Behavioral ratings at 7 years age: Peers rated EP/ VLBW's as significantly more sensitive/ isolated than controls Teachers rated EP/ VLBW's as significantly more inattentive than controls Parents rated EP/ VLBW's as more hyperactive than controls Significantly = P < 0.01	No data on funding source Data on neuromotor and intellectual functioning only collected once Data on behavior collected once
Robson 1997 9055145	• Developmental status and the quality of the home environment correlate with hyperactivity. • Medical risk, infant temperament, quality of home environment and developmental status correlate with attention. • A nurturing home environment fosters development of self-regulating behaviors in LBW.	Internal validity B
Breslau 1996 8836807	• LBW was significantly associated with ADHD but not with separation anxiety disorder, simple phobia, overanxious disorder, or oppositional defiant disorder. • Both the mothers' and teachers' ratings significantly correlated with increased ADHD in LBW infants and this relationship is stronger in urban than in suburban communities. • LBW children with the lowest IQ have highest incidence of ADHD. • The urban group was primarily black, more mothers had not completed high school and more were single. However, maternal marital status, history of substance abuse/dependence and smoking during pregnancy were not associated with ADHD.	Parent ratings, questionnaire results are biased but corroborated by teachers who are blinded to BW of children helps to corroborate. Internal validity B

Evidence Table 6A. Studies Evaluating Association of LBW to Behavioral Disorders
Part III

Author, Year	Associations found	Potential Biases
Breslau 2000 20298367	1) Information from mothers and teachers on children's **behavior problems** at age 11 revealed that the effect of LBW on attention problems differed between urban and suburban settings. 2) LBW children had an excess of **attention problems** in the urban disadvantaged communities and not in the suburban middle class communities. 3) LBW infants in the urban setting had twice as high incidence of attention problems than in urban NBW. 4) In suburban setting there was no difference in severe attention problems between LBW and NBW children. 5) LBW children had externalizing problems both in the urban and suburban settings (however this effect was mainly accounted for by maternal smoking in pregnancy). 6) No LBW effect was observed with respect to internalizing problems 7) Regardless of LBW status, maternal smoking during pregnancy was associated with an increase in externalizing problems 8) No association found between maternal smoking during pregnancy and internalizing or attention problems OVERALL SCORES — Attention scores — Internalizing — Externalizing MOTHER'S SCORES Urban • LBW (n=217) 58.8 52.7 52.2 • NBW (n=164) 55.8 51.5 50.4 Suburban • LBW (n=194) 55.1 50.4 48.4 • NBW (n=142) 53.8 48.6 46.3 TEACHER'S SCORES Urban • LBW (n=186) 56.9 50.3 53.9 • NBW (n=151) 54.7 48.8 48.5 Suburban • LBW (n=180) 53.7 49.0 48.5 • NBW (n=135) 54.0 48.7 48.3	1) Recollection bias: The Hx of maternal smoking during pregnancy was elicited when the child was 6 yrs old. This bias would have resulted in underestimation of the confounding effect of smoking during pregnancy. 2) Diagnosis bias: Although there was correspondence of the findings of teachers reports (who were blind to the LBW status of children) and the mothers reports, mothers report could have definitely been biased (worse scores from mothers of LBW infants)
Hille 2001 21319264	ELBW vs. Controls Total problem score: Boys: 3.3-9.8 points higher in ELBW vs. norm/ control Girls: 3.7-5.9 points higher in ELBW vs. norm/ control Social, thought, and attention difficulty scales were 0.5-1.2 SD higher in ELBW children vs. norm/control Internalizing and externalizing behavior scores: no difference for all 4 groups (except for one cohort for internalizing scores) ELBW children had higher total problem scores than normative/control children (statistical significance in European countries). Study identified similar types of behavioral problems in all 4 countries in ELBW infants. This suggests that problems with attention, social, and thought problems are a function of experiences of children who were born ELBW, and not to cultural differences.	(None) Study was privately funded

Evidence Table 6A. Studies Evaluating Association of LBW to Behavioral Disorders
Part III

Author, Year	Associations found	Potential Biases	
Katz 1996 97145056	Attention deficit is measured by the CPT test (error of omission). Hyperactivity and impulsivity is measured by the CPT test (error of commission). There were no differences among the preterm infants with mild, moderate and severe intracranial lesions. However, there was a significant increase in both errors of commission and omission in preterm with mild lesions compared to full term infants as well as in preterm with severe lesions compared to full term infants. With increasing severity of lesions in preterm infants, increasing percentage in each group commit errors of commission. Even in the absence of detectable intracranial lesions, preterm infants are still at higher risk for developing attention deficits than full term infants.	Exactly how FT controls were selected in an unbiased way is not described.	No data on funding source This study does not explore relationship of attention deficits identified with CPT test with actual school performance and achievement in this group of preterm infants. This study includes older preterm 26-34 weeks and does not include the extremely preterm 24-25 wk infants.

Evidence Table 6A. Studies Evaluating Association of LBW to Behavioral Disorders
Part III

Author, Year	Associations found			Potential Biases
Sajaniemi 1998 99041674	The neurological outcome of preterm infants was:			• Post hoc multiple comparisons were done between preterms and full terms for the multiple individual items of the tests used. • Cannot exclude selection bias • No matching between groups cannot exclude the presence of confounders. • Interactions between • Predictor may have masked some real associations; Possible interactions were not formally tested • Cannot exclude Diagnosis bias, as no information is given on the blinding of the personnel doing the outcome evaluation, of the child's PMHx.
	For Cerebral palsy:	Free from major disabilities	MDI	
	1) All prematures: 17.5%	82.5%	103	
	2) Prematures < 1000 gs: 23.5%	23.5%	98	
	3) Prematures > 1000 gs: 13.5%	85.6%	107	
	The developmental outcome: Preterm infants had significantly lower MDI scores when compared to full terms (Full terms 124) When temperament was considered: the premature children were significantly less active; more adaptive; less intensive; more positive in mood and had lower sensory threshold than the healthy control term children. When behavior was assessed (Infant's Behavior Records): the preterms were significantly less goal directed; less attentive, and had lower endurance than the controls. When Bayley neurodevelomental was assessed: 1) the preterms performed significantly less well than the controls. 2) Low Bayley scores correlated with temperament scores of high rhythmicity, positive mood, low persistence and high threshold 3) Low Bayley scores correlated with IBR scores 4) No strong relationship between temperament characteristics and cognitive performance. Preterm infants had significantly lower MDI compared to full terms: • Preterm infants were different in 5/9 items of temperament profile compared to full terms: less active ($p<0.008$), more adaptive ($p<0.02$), less intense ($p<0.01$), more positive in mood ($p<0.0004$), lower in threshold to respond ($p<0.0003$) • Preterm infants were different in 3/5 items in IBR profile when compared to full terms: less goal directed, less attentive, lower in endurance Predictors evaluation: • From the perinatal risk factors: preeclampsia, SGA, PVL and IVH were not associated with developmental outcome or temperament profiles. • PVL, IVH were associated with shorter attention span (1/5 items in IBR profile); when preterms compared to full terms. • Duration of NICU stay was not associated with Bayley score • Duration of ventilation was not associated with Bayley score • Duration of ventilation and days in NICU were associated with the 5 items of IBR profile; Duration of ventilation was associated with 1/9 items of temperament profile			

Evidence Table 6B. Studies Evaluating Association of LBW to School Performance and Learning Disabilities
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Hille 1994 8071753	Location: Netherlands Year of birth:1983 Description of group: VLBW Mean GA (range), wk: <32 weeks Mean BW (range), g: <1500 g Male: ND Race: ND Enrolled: 1338 Evaluated: 813 Number of sites: 1	Cases: Participants of the Project on Preterm and Small for Gestational Age Infants, a nationwide collaborative study 2) Perinatal data collection and follow-up until 2 years of age and assessments at 5 and 9 years 3) VLBW (very preterm) GA< 32 weeks at birth BW<1500 g.	ND	Cases: VLBW (or very preterm): 813 No control group	Prospective (single arm) cohort
Stathis 1999 99325758	Location: Australia Years of Birth: :1977-1986 Median GA (range), wk: 27.7(27.3-28.1) Mean BW (range), g: 860 (837-833) Male: 36% Race: ND Enrolled: 124 Evaluated: 87 Number of sites: 1	BW 500-999g survived to discharge Cared for in study NICU Enrolled in follow-up programs	ND	ELBW survived infants (87)	Prospective cohort (followed at 4, 8, 12, months)
Cherkes-Julkowski 1998 98262696	Location: ND Years of Birth: ND Mean GA (range), wk: ND Mean BW (range): Cases: 4.14±1.87 lbs Controls: 7.30±1.87 lbs Male: Cases: 61% Controls: 50% Race: ND SES: "middle class" Enrolled: 48 Evaluated: 28 (20 controls) Number of sites: 1	Preterm: <38 wks, BW<5 lbs, no congenital disorders, no retrolenteal fibroplasia, discharge from hospital prior to 42 wks conceptional age, mother willing to participate Controls: participats were enrolled in a longitudinal sudy before their second month of age	ND	Preterms (28) Controls: full term infants (20)	Retrospective cohort

Evidence Table 6B. Studies Evaluating Association of LBW to School Performance and Learning Disabilities
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Marlow 1993 8466264	Location: UK Years of birth:1980-1981 Description of group: VLBW Mean GA (range), wk: ND Mean BW (range), g: ≤1250 g Male: ND Race: ND Enrolled: 72 Evaluated: 51 Controls: 59 Number of sites: 1	Cases: VLBW ≤1250g at birth and without cerebral palsy at 6 years. Controls: 1) Control group (full term) matched for age, race, and sex, and school-matched.	Major disabilities (CP or major sensory impairment)	Cases: VLBW: 51 Controls: Full term/ controls: 59	Nonrandomized comparison trial

Evidence Table 6B. Studies Evaluating Association of LBW to School Performance and Learning Disabilities
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Hille 1994 8071753	General predictors: 1. BW 2. GA 3. Gender 4. Perinatal factors: congenital malformations, Apgar scores, intracranial hemorrhage, septicemia, assisted ventilation >7 days, serum bilirubin, thyroxine levels. 5. Socioeconomics 6. Performance at 5 years of age: Development, neuromotor function, speech/language, hyperactivity and school performance.	Assessment at 5 years of age: 1. Neurologic examination according to Touwen 2. Dutch test of speech and language development 3. Visual fields, acuity 4. Audiometry 5. Groningen Neurobehavioral concentration test 6. Child Behavior Checklist 7. Handedness 8. Kind of school 9. School results	At 9 years of age : School performance Special education	Questionnaire: kind of school (mainstream or special education), grade and need for extra help from teachers, remedial teaching, or speech therapy.
Stathis 1999 99325758	CNS Predictors 1) Other: head circumference category 2) Head growth velocity	Self-explanatory	**CNS:** Neurodevelopmental: Cognitive delay Behavioral disorders-ADHD School problems Learning disabilities	Academic problems--Answer questionnaires given to teacher ADHD--Dr. Paul rating scale McCarthy's scales
Cherkes-Julkowski 1998 98262696	General: GA Other: Mother perception of child competence	ND	**CNS:** Cognitive delay Neurodevelopmental School problem Neurological Impairment (NI) Attention Deficit Disorder (ADD) **Audiology:** Language	Cognitive delay, measured by Stanford-Binet School programs (school concerns = SC) Learning disabilities (LD) Neurological Impairment (NI) Attention deficit Disorder (ADD) Language impairment = LI – dx made by speech and language clinician

Evidence Table 6B. Studies Evaluating Association of LBW to School Performance and Learning Disabilities
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Marlow 1993 8466264	General predictors: VLBW	BW ≤ 1250g	At 8 years of age: School performance Behavior disorder	School performance: mathematics test (NFER Nelson), Schonell S1 graded word spelling test, Suffolk reading test, handwriting, fine motor skills. Behavior Measurements: parental questionnaire Rutter A(2), and teacher questionnaire using Rutter B(2) and Connors hyperactivity scale.

Evidence Table 6B. Studies Evaluating Association of LBW to School Performance and Learning Disabilities
Part III

Author, Year	Associations found	Potential Biases	Comments
Hille 1994 8071753	• School performance at 9 years of age is best predicted by performance at 5 years of age. • At 9 year of age, 19% were in special education and 81% in mainstream education. • At 9 years of age, only 44% of the nondisabled prematurely born children were in mainstream education at an age-appropriate level without special assistance. • GA <28 wks, BW < 1250 g, male gender and socioeconomics were significantly related to education outcome. Neonatal illnesses were not associated with school outcome at 9 years of age. • Majority of children having difficulty in school at 5 years of age had difficulty in school at 9 years of age.	Children labeled as having difficulty in school early in education (i.e. at 5 years of age) may continue to be treated as such within the system. Therefore independent evaluation of these children's performance at 9 years of age may reveal more useful information.	Internal validity A According to this study, early school problems are not transient.
Stathis 1999 99325758	Head circumference category at 8 months corrected age related to learning delay greater than one year when assessed at 6 years: HC Category / n / % with delay < 3rd percentile / 23 / 61% (39, 80) 3rd to 10th / 13 / 77% (46, 95) P = 0.004 > 10th / 40 / 30% (17, 47) Head circumference category at 12 months CA did predict McCarthy General Cognitive index at six years, but head circumference category at 24 months CA did not significantly predict McCarthy CGI at 6 years. Head circumference and head growth velocity was not shown to have a relationship with attention deficit hyperactivity disorder. *Head circumference category < 10th vs. greater than 10th percentile at four and 8 months corrected age were significantly associated with McCarthy CGI at 6 years age*	One nursery High rate of patients lost to follow-up (30%) Small numbers: limited ability to detect small differences; high chances of type 2 error	Study was privately funded
Marlow 1993 8466264	• Even in the presence of normal IQ, premature children are more likely to underachieve in school compared to full-term peers. • Forty-eight percent in preterm group had difficulty in one or more subjects compared with 19% in full term group. • Both teachers and parents report behavior problems of restlessness, hyperactivity, inattention, unresponsive/apathetic, fearful/afraid of new situations. • Motor difficulties and mathematics test best correlate with later school performance problems.		Internal validity B

Evidence Table 7. Studies Evaluating Association of LBW to Ophthalmologic Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Page 1993 94051493	Location: Canada Years of Birth: 1986-1987 Mean GA (range), wk: 27±1.8 (23-32) Mean BW (range), g: 942±197 (400-1250) Male: 38% Race: White 100% Enrolled: 138 Evaluated: 110 ? 50 Number of sites: 1	BW<1250 g admitted to Toronto's Hospital for sick children Survived the neonatal periods and had at least one eye examination between 28 and 42 of life that documented the severity of ROP	No 12-month follow-up reports	VLBW infants at 12-month follow-up (110) VLBW infants at 24-months follow-up (50)	Retrospective cohort (12, 24 months)
Cryo-ROP 1994 94304375 ***The original large population of CRYO-ROP**	Location: US Years of Birth: 1/1986 to 11/1987 Mean GA (range), wk: 26.0±1.9 to 29.6±2.1 Mean BW (range), g: 781±156 to 1061±144 Male: 48% Race: White 56%, Black 35%, Hispanic 6%, Other 3% Enrolled: 4099 Evaluated: 2759 Number of sites: 23	BW < 1251 g Survived at least 28 days No serious ocular anomaly, such as cataract, glaucoma, or chorioretinitis, and no major systemic malformations Parental consent Initial eye examination by a study-certified ophthalmologist by 49 days after birth	Death <28 days; serious ocular anomaly or systemic malformations, lack of consent; first eyes exam with 4 qd Death (264) Lost to follow-up (1076)	Zone and Stage of ROP (2759): Zone I (46) Zone II, stage 3+, 9-12 sectors (139) Zone II, stage 3+, 5-8 sectors (64) Zone II, stage 3+, 1-4 sectors (47) Zone II, stage 3 (241) Zone II, stage 2 (484) Zone II, stage 1 (500) Zone III (319) Other ROP (22) No ROP (896)	Prospective cohort (1 year)

Evidence Table 7. Studies Evaluating Association of LBW to Ophthalmologic Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Keith 1995 95288128	Location: UK Years of Birth: 1977-1992 Mean GA (range), wk: Sample 1: 26.0±2.3 Sample 2: 26.1±2.2 Mean BW (range), g: Sample 1: 783±136 Sample 2: 786±133 Male: ND Race: ND Enrolled: 457 Evaluated: 434 Number of sites: 1	ELBW infants, BW < 1000g Survival to hospital discharge Eye exams done	ND Not seen by the ophthalmologist: transferred to another level-3 center for ongoing care (17); unknown reasons (6)	Sample 1: ELBW survivors born 1977-1984 (145) Sample 2: ELBW survivors born 1985-1992 (312)	Prospective cohort (16 years)
Foreman 1997 97271716	Location: UK Years of Birth: 4/1994-4/1996 Mean GA (range), wk: Cases: 29.38 Controls: 39.88 Mean BW (range), g: Cases: 1413±302 Controls: 3437±625 Male: 63% Race: ND Enrolled: 114 Evaluated: 16 (16 controls) Number of sites: 1	Healthy preterm infants GA 27 –32 weeks; weight within the normal range for GA Normal on all criteria of Standard child health surveillance program from 7.5 to 48 months Each could be matched with FT control on gender, post-natal age at testing, and on SEC. Healthy controls from School population Controls: children drawn from a school population who were known to have been full-term, normal delivered and whose uneventful medical and developmental histories were confirmed by parents, general practitioners, and teachers	ND	Healthy preterm infants (16) Controls: Matched full term controls (16)	Prospective cohort (6.1 years)

Evidence Table 7. Studies Evaluating Association of LBW to Ophthalmologic Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Tin 1998 99046171 ***also in CNS table**	Location: North of England Years of Birth: 1983, 1990-1991 Median GA (range), wk: ND Mean BW (range), g: ND Male: ND Race: ND Enrolled: 1983 (230); 1990-1 (566) Evaluated: 1983 (230); 1990-1 (566) Number of sites: 5	GA 23-31 weeks	ND	1983 cohort (230): Child reviewed without difficulty (204) Child traced with difficulty (14) Child seen with difficulty after child was traced (12) 1990 to 1991 (566): Child reviewed without difficulty (505) Child traced with difficulty (26) Child seen with difficulty after child was traced (35)	Prospective cohort *2 Cohorts of different time periods
Dogru 1999 99168711	Location: Japan Years of Birth: 4/1994-4/1996 Mean GA (range), wk: Sample 1: 27.6±2.9 Sample 2: 26.9±1.4 Sample 3: 26.3±3.1 Controls: 29.6±2.6 Mean BW (range), g: Sample 1: 1016±207 Sample 2: 836±178 Sample 3: 874±218 Controls: 1193±241 Male: 49% Race: ND Enrolled: 144 Evaluated: 78 (66 controls) Number of sites: 1	Premature infants (BW < 1500 g, GA < 37 weeks) with ROP Controls: randomly selected premature subjects with no ROP	Physical and mental disabilities or any CNS and ocular disorder	Premature infants: (Sample 1, 2, and 3): Premature infants with ROP (78) Sample 1: ROP stage 1 (53) Sample 2: ROP stage 2 (11) Sample 3: ROP stage 3 (14) Controls: Premature infants without ROP (66)	Prospective cohort (18-24 months)

Evidence Table 7. Studies Evaluating Association of LBW to Ophthalmologic Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Pennefather 1999 20002011 Pennefather 2000 20217908 *** This study also should be mentioned in multiple outcome and CNS table**	Location: UK Years of Birth: 1/1/90-12/31/91 Mean GA (range), wk: ND Mean BW (range), g: ND Male: ND Race: ND Enrolled: 566 Evaluated: 558 Number of sites: ND	All surviving children <32wk GA born in geographically deprived region in Northern UK Survived to 2 years old	No examined at age 2 years old	Preterm infants (558)	Prospective cohort and retrospective review of patient records (2-3 years)
Tin 2001 21143595 ***1990-1991 sample is same as 99046171**	Location: North of England Years of Birth: 1990-1994 Median GA (range), wk: 23-27 Mean BW (range), g: ND Male: ND Race: ND Enrolled: 1990-1 (781); 1992-1994 (ND) Evaluated: 249 (for current review) Number of sites: ND	GA < 28 weeks Surviving (born 1990-1991) when 2 years old Surviving (born 1992-1994) when 18 months Assessed for CP and ophthalmic For current review, only SpO_2 88-98% and SpO_2 70-90% groups were included	ND	Sample 1: Preterm infants, SpO_2 88-98% (123) Sample 2: Preterm infants, SpO_2 70-90% (126)	Prospective cohort

Evidence Table 7. Studies Evaluating Association of LBW to Ophthalmologic Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Page 1993 94051493	*General predictors:* 1) Birth weight 2) GA *CNS predictors:* 1) Intracranial/ Intraventricular hemorrhage 2) Periventricular leukomalacia *Ophthalmology predictors:* 1) Retinopathy of prematurity 2) Myopic at 12 months post-term *Cardiovascular or pulmonary predictors:* 1) PDA 2) Days ventilated 3) Days in O_2	ROP - ICROP Others not defined Myopic - >0.25 D	**Ophthalmology outcomes:** Visual impairment Strabismus Refractive error Myopia Astigmatism	Myopia - spherical equivalent of ? 0.25 diopters High Myopia - spherical equivalent of ? 4.0 diopters Astigmatism - > 1 diopter in any meridian or cycloplegic refraction Anisometropia - spherical equivalent >2 D between eyes (both refracted)
Cryo-ROP 1994 94304375 ***The original large population of CRYO-ROP**	*Ophthalmology predictors:* Retinopathy of prematurity	ROP defined by examination according to the ICROP	**Ophthalmology:** Visual impairment Structural outcome	ROP outcomes (structural): I. Only peripheral changes, no mascular distortion II. Mascular displacement III. Retinal fold involving macula IV. Retrolental opacity entotal retinal detachment and/or total pupillary occlusion to retinal detachment Functional outcome: a. Normal fixation b. Presence/absence of nystagmus c. Strabismus d. Refractive error (spherical equivalence)

Evidence Table 7. Studies Evaluating Association of LBW to Ophthalmologic Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Keith 1995 95288128	*General predictors:* Birth cohort: 1977-1984 vs. 1985-1999	ND	***Ophthalmology outcomes:*** 1) blindness 2) severe ROP	Eye exam with ICROP classification. Sheridan-Gardner test - visual outcome. Snellen's eye chart - visual outcome.
Foreman 1997 97271716	GA	28-32 week prematurity vs. full term controls	**CNS** Attention skill **Ophthalmology** Visual-perceptual skills Visual-motor skills	Point-to-Target test Complex visual search test Cartoon comparison test Overlapping figures Goillin incomplete figures
Tin 1998 99046171 ***also in CNS table**	General: GA (23-31 wks)	ND	**CNS: CP** Neurodevelopmental: Mental retardation (IQ < 75) Other; disability (severe, sever sensorimotor) Other: development - assessed by Griffith's mental and developmental scales **Ophthalmology** Visual impairment Blindness Other: Severe ROP with Cryotherapy	Definition of "severe disability" and "severe sensorimotor disability" were not given in this article . They referred to the wrong reference for these definitions, therefore, I am unable to find the definitions. Reference population for Griffith's scales were "preterm babies in the study S serious sensorimotor disability"
Dogru 1999 99168711	ROP	Staging of retinopathy was based on International Classification of Retinopathy of Prematurity (The Committee for the Classification of Retinopathy of Prematurity, 1984)	**Ophthalmology:** Visual acuity	Preferential looking method

Evidence Table 7. Studies Evaluating Association of LBW to Ophthalmologic Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Pennefather 1999 20002011 Pennefather 2000 20217908 *** This study also should be mentioned in multiple outcome and CNS table**	*General Predictor:* GA CNS: 1) IVH 2) Periventricular leukomalacia 3) Ventriculomegaly/Ventricular Dilation Ophthalmology: 1) ROP 2) Refractive error Other: Family Hxg strabismus, Developmental disability, CP	ND	**CNS:** Cerebral palsy **Ophthalmology:** Visual impairment (cortical)(CVI) Cicatricial ROP Strabismus	Retrospective review of patient records Visual acuity, visual fields
Tin 2001 21143595 ***1990-1991 sample is same as 99046171**	*General predictors:* GA *Other predictors:* SpO_2 policies (88-98% vs.70-90%)	SpO_2 policies were obtained retrospectively	**CNS:** Cerebral palsy **Ophthalmology**: Blindness Severe ROP Rx with cryotherapy	Threshold ROP: (Cryo-ROP definition) stage 3 plus acute ROP extensive permanent cicatricial retinal scanning

Evidence Table 7. Studies Evaluating Association of LBW to Ophthalmologic Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Page 1993 94051493	Outcome: Incidence of myopia at 12 mo postterm age: Overall incidence of myopia in cohort (BW<1251 g) was 15% (4.5% severe myopia) At 12 months age: Increased severity of ROP predicted increased severity of myopia (p=0.001) Overall, 16% of infants had myopia, and 4.5% had severe myopia at 12 months age. To show incidence of myopia according to severity of ROP: 10% of infants with No or Stage 1 ROP had myopia 54% of infants with Stage 3 ROP had myopia 23% of infants with Stage 3 ROP had severe myopia The likelihood of myopia at 12 months age doubled with each increment in ROP stage. - At 24 months age: 80% of 50 children showed deteriorating vision. - 13 of 16 (81%) showed worsening of their myopia after 12 months age. Overall, the incidence of myopia and severe myopia increased among 50 infants followed to 2 years: 38% had myopia 0.25-4 Diopters; 24% had myopia >4 Diopters. BW was negatively associated with incidence of myopia (p=0.002). BW<750 g 3.2 fold odds of myopia vs. 751-1000 g. - BW <750 g 10 fold odds of myopia vs. 1001-1250 g. Incidence of strabismus was positively associated with severity of ROP (e.g. no ROP 6% vs. Strabismus at 12 mo in infants who had Stage 3 ROP 38%). There was further increased diagnosis of strabismus at 24 months age. Months of age in infants who had had Stage 3 ROP (38% to 62%). 100% of infants who had Grade III or IV IVH had strabismus	Retrospective NB and ophthalmic chart review 36% eye reports available at 24 months. Also 24 month sample was biased toward children at greatest risk of myopia. Children with normal eye results at 12 months age were discharged from further follow-up at 18 months post-term age. This may have led to underdiagnosis of myopia due to lack of detection of progressive myopia. Infants born 1986-1987 (not a bias, but a limitation) Used other pop reference figures for norms	No data on funding source This study demonstrates the importance of low birth weight, ROP severity, and IVH in the development of myopia and strabismus.

Evidence Table 7. Studies Evaluating Association of LBW to Ophthalmologic Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Cryo-ROP 1994 94304375 ***The original large population of CRYO-ROP**	The more posterior the zone of ROP and /or the greater the extent of Stage 3+ ROP, the worse the structural and functional ophthalmic outcomes. Zone II without plus disease, Zone III, or no ROP was associated with low rate of unfavorable outcome. CNS injury may affect ophthalmic function (e.g. nystagmus and strabismus). Visual function by ROP Classification ICROP Abnl.Fixation %Nystagmus %Strabismus Zone I ……44% ……6%……25% Zone II Stage 3, 9-12 sectors 57%……39%……33% Zone II, Stage 1……2%……1%……10% No ROP……1% ……1%……6% % of Eyes with refractive error (≥2 diopters myopia) by ROP severity No or Stage 1 ROP (<5%) Zone II, Stage3+, 9-12 sectors (62%) Zone I (40%)	(None)	Study was government and privately funded Biweekly or weekly eye exams until fully vascularized or until threshold ROP (>5 contiguous or 8 cumulative clock hours) stage 3 with plus disease. Only data from eyes that served as controls (untreated) are included in this segment.
Keith 1995 95288128	**Any ROP:** Birth Cohort 1977 –1984 (141) 68/141 48.2 % 1985-1992 (293) 105/293 35.6% OR=0.60 (0.40-0.90) P<0.02 **Severe ROP:** 1977 –1984 (141) 36/141 25.4 % 1985-1992 (293) 52/293 17.4% OR=0.62 (0.38-1.02) NS **Blindness:** 1977 –1984 (141) 2/141 1.4 % 1985-1992 (293) 2/293 0.6% OR=0.43 (0.05-3.5) NS	Data are from care center No outborn infants in either cohort so data are not generalizable to outborn ELBW infants Twenty-three surviving ELBW's could not be located to determine ROP status.	No data on funding source 16 year study; 1001 ELBW infants; 457 survived to discharge; 434 seen by same ophthalmologist. Twenty children not seen by ophthalmologist.

Evidence Table 7. Studies Evaluating Association of LBW to Ophthalmologic Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Foreman 1997 97271716	***Visual-motor coordination:*** PT v. FT NS diff **Visual-spatial attention skill**: Significant difference between Preterm and Full term in complex visual search scores (failure to find figure and latency to find) and cartoon comparisons PT 2.94 FT 0.81 P<0.05 ***Visual-form perception***: NS difference between Preterm and full term in latency to respond to overlapping figure and Gollin incomplete figure tests. PT 22.2% FT 21.9% NS diff Compared to matched, FT controls, the PT school age group performed poorly on 2 measures visual-motor tests. Thus in the absence of detectable disability, prematurity is associated with visual-motor and attentional impairments that persist through 16 years age.	Small sample size Incomplete data analysis	No data on funding source
Tin 1998 99046171 ***also in CNS table**	*Result of 1983 cohort at 6 years:* ***Severe disability:*** Sample 1: 4.4%, Sample 2 : 2.1%, Sample 3: 50% *IQ < 75 without sensorimotor disability:* Sample 1 : 4.9%, Sample 2 : 0, Sample 3 : 25% *Severe sensorimotor disability:* Sample 1 : 5.9%, Sample 2 : 21.4%, Sample 3 : 41.7% *Severe sensorimotor or cognitive disability:* Sample 1 : 8.4% (5 - 13.1%, 95% CI) Sample 2 : 21.4% (4.7-50.8%) Sample 3: 41.7% (15.2-72.3%) **Result of 1990 cohort at 2 years:** *Severe disability:* Sample 1: 7.9%, Sample 2: 15.4%, Sample 3: 57.1% **High f/u rate is critical because it may underestimate incidence of the outcome.**	No definitions of outcome, incomplete methods description, wrong reference	Study was privately funded
Dogru 1999 99168711	Stage 3 ROP had significantly lower visual acuity scores compared to stage 1-2 or no ROP at 18-24 months (P<0.0001)	(None)	No data on funding source

Evidence Table 7. Studies Evaluating Association of LBW to Ophthalmologic Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Pennefather 1999 20002011	Strabismus in 70/558 (12.5%) infants GA<32 week . **The incidence of strabismus increased with decreasing** GA (p=0.0004), increasing severity of ROP (p=0.0001), and decreasing general developmental quotient (GMDS) (p<0.0001).	Prospective evaluation but retrospective collection of neonatal data; therefore, probable incomplete collection of variable reason for present and absent data	No data on funding source
Pennefather 2000 20217908 *** This study also should be mentioned in multiple outcome and CNS table**	Stabismus present in 28 (52%) of patients with CP (P< 0.001) **OR (95% CI) of Strabismus if following predictor was present:** Cicatricial ROP: 4.94 (1.1-22.12), p0.037 Fam Hx of Strabismus: 4.15 (2.19-7.88), p<0.00005 Refractive Error: 2.71 (1.3-5.66), p=0.008 GMDS 78-100: 3.34 (1.46-7.64), p =0.004 GMDS <77: 46.2 (17.1-125), p<0.00005 This study confirms findings of other studies that strabismus is increased in premature infants with decreasing GA and is increased with increasing severity of ROP and CP. Independent factors related to strabismus are cicatricial ROP, refractive error, family hx of strabismus, and developmental delay (especially delayed hand-eye coordination)	No demographic data was report (the cohort was described elsewhere)	
Tin 2001 21143595 ***1990-1991 sample is same as 99046171**	Premature infants who had oxygen saturation range (SpO2) between 88-98% for at least first 8 weeks of life developed severe ROP requiring treatment with cryotherapy four times greater than infants who had SpO2 range between 70-90. Incidence of severe ROP with Cryotherapy (SpO2 range 88-98%)=28% Incidence of severe ROP with Cryotherapy (SpO2 range 70-80%)= 6% Incidence of Blindness in the two study groups: Premature infants with SpO2 range 88-98%: 4 / 65 Premature infants with SpO2 range 70-80%: 0 / 65 Incidence of CP in the two study groups: Premature infants with SpO2 range 88-98%: 17% Premature infants with SpO2 range 70-80% 15% The lower SpO2 range was not associated with difference in CP. Differences in SpO2 policies (70-90% vs. 88-98%) did have a major impact on the proportion who developed severe ROP, but had no effect on survival or on incidence of CP among premature survivors.	Different pulse oximeters No attempt to document real SpO_2 or how often SpO_2 fell outside recommended ranges (or vice versa). Narrow limits broached often > wider limits.	ROP screening conformed to national guidelines

Evidence Table 8. Studies of Treatment Effects for LBW Infants with Retinopathy of Prematurity (ROP)
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Cryo-ROP, 1990, 1996, and 2001 (x3) 91024693, 96180078, 21375786, 21375787, 21375788 Repka 1998 98426775 ***sample from the large population of 94304375 (CRYO-ROP)**	Location: US Years of Birth: from 1/1986 to 11/1987 Mean GA (range), wk: 1 yr follow-up: 26.3±1.8 5.5 yr follow-up: 26.3±1.7 (bilateral threshold ROP; 26.3±1.8 (asymmetric threshold ROP) 10 yr follow-up: 26.3±1.8 Mean BW (range), g: 1 yr follow-up: 800±165 5 yr follow-up: 801±165 (bilateral threshold ROP; 800±165 (asymmetric threshold ROP) 10 yr follow-up: 800±165 Male: ND Race: ND Enrolled: 291 Evaluated: 246 (at 1-year exam), 234 (at 5.5-year exam), 247 (at 10-year exam) Number of sites: 23	BW < 1251 g Survived at least 28 days Diagnosis of threshold ROP	ND {(At 1-year follow-up: Died before the 1-year follow-up (36) Unable to follow-up for the 1-year exam (14) At 5.5-year & 10-year follow-up: Died before the 5.5-year & 10-year exam (36)} Lost to follow-up for the 10-year exam (8)	At 1-year exam: VLBW infants with ROP (241) At 5.5-year exam: VLBW infants with ROP (234) – bilateral threshold ROP (191); asymmetric threshold ROP (43) At 10-year exam: VLBW infants with ROP (234)	Randomized controlled trial (1, 5.5, 10 years)
Cryotherapy for Retinopathy of Prematurity Group 1993 93191597	Location: US Years of Birth: 1986-1987 Mean GA (range), wk: 26.3±1.8 Mean BW (range), g: 800±165 Male: ND Race: ND Enrolled: 236 Evaluated: 236 Number of sites: 23	All infants <1251g, who participated in CRYO-ROP Multicenter trial and had threshold (severe) ROP.	See original study	Infants with threshold ROP (236)	3.5 years

Evidence Table 8. Studies of Treatment Effects for LBW Infants with Retinopathy of Prematurity (ROP)
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Algawi 1994 95001766	Location: UK Years of Birth: Sample 1: 2/1992-11/1992 Sample 2: 1/1987-2/1992 Mean GA (range), wk: Sample 1: 24-32 Sample 2: 25-30 Mean BW (range), g: Sample 1:700-1200 Sample 2: 620-1500 Male: 53% Race: ND Enrolled: 32 Evaluated: 32 Number of sites: 1	Premature infants with threshold ROP (stage 3+ disease of 5 or more contiguous clock hours [30° sector] or 8 cumulative clock hours) or more	ND	Sample 1: Laser Treatment (12) Sample 2: Cryotherapy Treatment (20)	Prospective cohort
Ling 1995 95391616	Location: UK Years of Birth: 1992-1993 Median GA (range), wk: 25.5 (24-27) Median BW (range), g: 725 (589-887) Male: 38% Race: White 100% Enrolled: 13 Evaluated: 13 Number of sites: 1	All premature infants in 1 unit who developed threshold ROP and treated with diode laser therapy	ND	Infants with ROP treated with Diode laser (13)	Before and after trial (6, 12, and 18 months)

Evidence Table 8. Studies of Treatment Effects for LBW Infants with Retinopathy of Prematurity (ROP)
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Connolly 1998 984267776	Location: US Years of Birth: 11/1989-5/1992 Mean GA (range), wk: 25.4 (23-32) Mean BW (range), g: 731 (440-1318) Male: 44% Race: ND Enrolled: 52 Evaluated: 25 Number of sites: 1	Premature infants with symmetric threshold ROP underwent bilateral treatment	ND (Stage 4 or 5 ROP in one or both eyes Refused to cooperate with monocular occlusion during Snellen testing Limited cognitive ability that precluded Snellen or illiterate e-chart acuity testing)	Sample 1: Laser Treatment (21 eyes) Sample 2: Cryotherapy Treatment (21 eyes)	RCT and follow-up (5.8 [4.3-7.6] years)
Shalev 2001 21331013	Location: US Years of Birth: 1991-1992 Mean GA (range), wk: 24.8 (23.4-27.0) Mean BW (range), g: 631 (540-846) Male: 60% Race: 30% Enrolled: 19 Evaluated: 10 Number of sites: 1	Threshold ROP treated with laser or cryotherapy	ND Lost to follow-up (2) Died at 4 months of age (2) Refusal (3)	Infants with threshold ROP (10)	RCT with prospective follow-up (7 years and 6 months)
O'Connor 2002 21635822	Location: UK Years of birth: 1985-1987 Mean GA (range), wk: 31.06±3.09 Mean BW (range), g: 1400 (iqr 1150, 1562) Male: ND Race: ND Enrolled: 505 Evaluated: 505 Number of sites: 5	All infants <1701g, who survived 3 weeks. Born to mothers who were residents in the study areas, admitted to one of 5 NICUs.	ND	Premature infants (254) Control (169)	10-12 years

Evidence Table 8. Studies of Treatment Effects for LBW Infants with Retinopathy of Prematurity (ROP)
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Cryo-ROP, 1990, 1996, and 2001 (x3) 91024693, 96180078, 21375786, 21375787, 21375788 Repka 1998 98426775 ***sample from the large population of 94304375 (CRYO-ROP)**	*Ophthalmology predictors:* Threshold retinopathy of prematurity At 5.5-year & 10-year follow-up: Cryotherapy vs. No Cryotherapy	At least 5 contiguous clock hours or 8 cumulative clock hours of stage 3 ROP in zone 1 or 2 in the presence of "plus disease" (dilation and tortuosity of the posterior retinal vessels) Monocular visual acuity (using log of minimal angle of resolution visual acuity chart)	**Ophthalmology:** Visual impairment (visual acuity) Structural outcome Blindness Distance snellen acuity Near snellen acuity Visual field Medical and surgical ophthalmologic interventions Cerebrospinal fluid shunting surgery	Visual acuity - • "normal": ?1.6 cycles per degree • "below normal": 8.0 to <1.6 cycles per degree • "poor": <0.8 cycles per degree • "blind": eyes judged to have no light perception, eyes for which the tester was unable to estimate acuity, which were judged by a physician to have total retinal detachment Structural outcome - • Posterior retinal fold • Retinal detachment involving zone 1 of the posterior pole • Retrolental tissue or "mass" obscuring the view of the posterior pole Favorable Functional outcome: Favorable visual acuity: better than 20/200 Unfavorable visual acuity: worse than 20/200 or blind Goldmann perinmetry to measure visual field extent along 8 meridian using V4e and III 4 e stimuli
Cryotherapy for Retinopathy of Prematurity Group 1993 93191597	Retinopathy of Prematurity (ROP) (Specifically threshold ROP treated with cryotherapy or no cryotherapy)	Threshold ROP as per CRYO-ROP definition.	**Visual impairment** Blindness	Visual acuity (HOTV, Grating) Unfavorable outcome (HOTV 20/200 or worse, Grating <6.4 cycles per degree; blind): this outcome is combination of poor + blind Myopia:≥2 <6 diopters; ≥6 diopters

Evidence Table 8. Studies of Treatment Effects for LBW Infants with Retinopathy of Prematurity (ROP)
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Algawi 1994 95001766	Ophthalmology Retinopathy	ND	**Ophthalmology:** Visual impairment: Refractive error Visual fixation Preferential looking	Visual functions were assessed by either fixation pattern or preferential looking technique
Ling 1995 95391616	ROP	Threshold as for Cryo-ROP trial	**Ophthalmology** Visual function	Favorable outcome (anatomical) defined as a normal posterior funus on BIO exam performed by observer who had not done Rx. Functional outcomes assessed using Keeler preferential looking cords acuity greater or equal to 0.8 cycles per degger defined 1 yr. Age .
Connolly 1998 984267776	ROP	Threshold as for Cryorop trial - 5 or more contiguous or 8 cumulative clock-hours of stage 3 ROP in zone I or II in the presence of “plus” disease	**Ophthalmology Outcomes:** Visual impairment Refractive error Visual acuity	Visual acuity 20/50 or better =good Visual acuity 20/60 or worse = poor
Shalev 2001 21331013	ROP	Threshold as for Cryorop trial	**Ophthalmology** Visual function outcome Structural outcome	Favorable outcome = normal posterior fundus. Refraction by retinoscopy Functional outcomes: Keeper preferential looking cards . Favorable function was grating acuity greater than or equal to 0.8 cycles/degree (as per CRYO ROP study at 1 year)

Evidence Table 8. Studies of Treatment Effects for LBW Infants with Retinopathy of Prematurity (ROP)
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
O'Connor 2002 21635822	Birth weight ROP	BW self-explanatory (grams) ROP not stated, but c/w ICROP	**Visual impairment** Blindness	Visual acuity: Normal (20/20); ≥Moderately reduced = worse than 20/40. Contrast sensitivity (Pelli Robson chart) Steroacuity (TNO plates) Perimetry (visual fields) (Damato campimeter) Color vision (desaturated D15 test) Strabismus (cover test and prism test) Refractive error (cycloplegic refraction) Eye size and dimensions of its components (N.D.)

Evidence Table 8. Studies of Treatment Effects for LBW Infants with Retinopathy of Prematurity (ROP)
Part III

Author, Year	Associations found	Potential Biases	Comments
Cryo-ROP, 1990, 1996, and 2001 (x3) 91024693, 96180078, 21375786, 21375787, 21375788 Repka 1998 98426775 ***sample from the large population of 94304375 (CRYO-ROP)**	**<u>At 1-year follow-up:</u>** Fundus photography: Unfavorable posterior pole outcome at 1 yr Cryotherapy Rx 191 eyes 25.7% Control 194 eyes 47.4% P<0.001 Unfavorable structural outcome (retinal detachment, macular fold, etc) at 1 yr Cryotherapy Rx 208 eyes 49% Control 203 eyes 66% Unfavorable functional (Teller Visual Acuity) outcome at 1 yr Cryotherapy Rx 160 35% Control 158 56.3% **<u>At 5.5-year follow-up:</u>** Visual acuity Unfavorable outcome: Threshold ROP (control: no cryotherapy) 62% Threshold ROP CRYOtherapy 47% Greater reduction in unfavorable visual acuity outcome in cryo group (P<0.005) **Unfavorable structural outcome** Threshold ROP (control: no cryotherapy) 45% Threshold ROP CRYOtherapy 27% Greater reduction in unfavorable structural outcome in cryotherapy group (P<0.001) **Blindness** Threshold ROP (control: no cryotherapy) 48% Threshold ROP CRYOtherapy 32% Greater reduction in blindness in cryotherapy group (P<0.001) **Visual acuity 20/40 or better** Threshold ROP (control: no cryotherapy) 17% Thresdhold ROP CRYOtherapy 13% No significant difference between groups with respect to proporation of infants with visual acuity 20/40 or better (P=0.19). Among children who had Threshold ROP treated with cryotherapy: 226 / 257 had ocular intervention in addition to cryotherapy (0.9% interventions per child) Vitrectomy 26% (66/257); Scleral buckling 3% (8/257); Lensectomy 18%; Glaucoma medical treatment 4%; Glucoma surgery 2%; amblopia treatment 20%; Strabismus surgery 10%; Cataract surgery 2%; Enucleation 2%; Ventriculoperitoneal shunt (VPS) 11% Among children in the Natural History Cohort with variable ROP: 239 ocular interventions (0.4% interventions per child) Strabismus 6%; Amblyopia Rx 7% (3% if no ROP); VPS 3%	(None)	Study was government and private funded 5 ½ year follow-up of preterm infants with BW <1251 g with Threshold ROP randomized to cryotherapy vs. no cryotherapy groups. Both had high incidence of blindness, impaired visual acuity, and unfavorable outcome. Unfavorable outcomes were significantly less in cryotherapy group vs. control group. Excellent long-term (10 yr) ophthalmic follow-up of PT infants with severe ROP. Cryotherapy assoc with significantly less unfavorable visual function outcome and less unfavorable structural outcome. >44% of cryo Rx eyes have unfavorable visual outcome and 62% have unfavorable structural outcome. Threshold ROP with or without Rx is high for adverse long-term outcome. Infants with BW<1251 g with ROP underwent a large number of ophthalmic interventions through the first 5.5 years of life. Long-term costs of extreme prematurity and ROP include initial ablative therapy for ROP and societal loss due to visual impairment or blindness and ongoing costs for caring for eye problems.

Evidence Table 8. Studies of Treatment Effects for LBW Infants with Retinopathy of Prematurity (ROP)
Part III

Author, Year	Associations found	Potential Biases	Comments
Cryo-ROP, 1990, 1996, and 2001 (x3) 91024693, 96180078, 21375786, 21375787, 21375788 Repka 1998 98426775 **Continued**	**<u>At 10-year follow-up:</u>** **Unfavorable** Visual outcomes (functional) in Threshold ROP. Comparison of Threshold ROP eyes treated with CRYO vs. Control. Distance Snellen Acuity (≥20/200) CRYO Rx 44% Control 62% Near Snellen Acuity CRYO Rx 43% Control 62% Blindness CRYO Rx 33% Control 50% Unfavorable Visual Acuity Zone I/Threshold ROP/ CRYO Rx 94% Zone I/Threshold ROP/Control 94% Unfavorable structural outcome Zone I/Threshold ROP/ CRYO Rx 88% Zone I/Threshold ROP/Control 94% Although cryotherapy was beneficial in reducing unfavorable structural and functional outcome vs. no treatment in Threshold ROP eyes, infants with threshold ROP still were at high risk for unfavorable outcome even with cryotherapy, especially infants with Threshold Zone 1 ROP.[Vii] Visual fields at 10 years age in children enrolled in the CRYO ROP trial who had history of Threshold ROP (cryotherapy vs. control). Visual fields (with or without cryotherapy) were significantly smaller with severe ROP Visual fields in treated eyes were reduced by 30-37% vs. no ROP. Visual fields in control eyes were reduced by 27-33% compared to no ROP. Cryotherapy vs. control preserved sight and visual field in infants with severe ROP. Visual field area was 24 to 26% larger in CRYO Rx eyes vs. Control. Comparison of sighted treated eyes vs. sighted control eyes revealed that cryotherapy reduced visual field by small amount (5%).		

Evidence Table 8. Studies of Treatment Effects for LBW Infants with Retinopathy of Prematurity (ROP)
Part III

Author, Year	Associations found						Potential Biases	Comments
	Predictors/ Conditions	N	Outcome Category	Outcome of Interest/ Instruments used	% with Outcome	Methods of Correlation		
Cryotherapy for Retinopathy of Prematurity Group 1993 93191597	Cryotherapy	203	vision	Unfavorable outcome HOTV acuity	47%	Cryo group had 19% reduction in unfavorable outcome for HOTV (p<0.01)		
	No Cryotherapy	203	vision	Unfavorable outcome HOTV acuity	58% unfavor-able outcome			
	Cryotherapy	193	vision	Unfavorable outcome Grating acuity	52%	Cryo group had 20% reduction in unfavorable outcome for grating (p<0.01)		
	No Cryotherapy	193	vision	Unfavorable outcome Grating acuity	66%			
	Cryotherapy		vision	Myopia **:** 3 **2 <6 diopters**	20%	More treated eyes had myopia than control eyes. Data not shown is that more control eyes could not be refracted.		
	No Cryotherapy		vision	Myopia **:** 3 **2 <6 diopters**	15.5%			
	Cryotherapy		vision	**Myopia** 3 **6 diopters**	37.7%			
	No Cryotherapy		vision	Myopia **:** 3 **6 diopters**	27.2%			

Evidence Table 8. Studies of Treatment Effects for LBW Infants with Retinopathy of Prematurity (ROP)
Part III

Author, Year	Associations found	Potential Biases	Comments
Algawi 1994 95001766	Myopia Treat with Laser 6/15 (40%) (Spher Equiv –1.5 to –3.5 D) Treat with Cryotherapy 23/25 (92%) (Spher Equiv –0.5 to –8.0 D) Significantly more myopia in cryotherapy vs. laser group (P=0.0006) Hypermetropia <+3.0 Diopters Treat with Laser 9/15 (60%) Treat with Cryotherapy 2/25 (8%) Clinical significant astigmatism (no significant difference between groups (P=0.4). Treat with Laser 5/15 Treat with Cryotherapy 5/25	Small sample size Cohorts treated at different time, not concurrent and not randomized	No data on funding source There is a high incidence of myopia following treatment for threshold ROP. Myopia occurred less often in the laser treated group vs. cryotherapy treated group.
Ling 1995 95391616	Visual outcome of Threshold ROP treated with diode laser: Structural Outcome (as defined by Cryotherapy Multicenter Trial) at 19.5 months age (range 9.7-25.5. mo) was favorable in all 13 patients (25 eyes). Functional outcome at the same follow-up (n=13): 3 with strabismus; 1 myopic; grating visual acuity (Keeler preferential looking cards) ranged 2.9-14.5 cycles per degree. 7 uniocular and 6 binocular acuity assessments fell within the CRYO-ROP definition of favorable acuity at 1 year of age ($\geq$0.8 cycles per degree uniocular)	(None)	No data on funding source

Evidence Table 8. Studies of Treatment Effects for LBW Infants with Retinopathy of Prematurity (ROP)
Part III

Author, Year	Associations found	Potential Biases	Comments
Connolly 1998 984267776	Laser Treated Threshold ROP / Cryotherapy Treated Threshold ROP / Total Visual Acuity 20/50 or better: 17 / 8 / 25 Visual Acuity 20/60 or worse: 4 / 13 / 17 Total: 21 / 21 / 42 81% of laser-treated vs. 38 % of cryotherapy treated Threshold ROP had good visual acuity outcome (VA 20/50 or better). The odds that a laser treated eye had a good visual outcome were 6.91 greater than threshold ROP eyes treated with cyrotherapy (95% CI 1.7- 28). Refractive Error: On average, 23 cryotherapy eyes had a mean spherical equivalent of – –5.08 Diopters vs. –3.05 Diopters for 23 laser treated eyes P=0.0072). Thus, cryotherapy eyes had greater amount of myopia than laser treated eyes. Summary: The odds that eyes treated with laser therapy would have best-corrected visual acuity of 20/50 or better was almost 7 times greater than cryotherapy treated eyes. Also, laser treated eyes had less myopia than cryotherapy treated eyes. Thus, the results suggest that laser photocoagulation for threshold ROP was more likely to result in good visual outcome with less myopia compared to cryotherapy treatment.	Excluded large numbers of subjects	No data on funding source
Shalev 2001 21331013	**Associations:** All 10 Laser treated eyes had favorable structural outcome; 2 of 8 cryotherapy eyes had unfavorable structural outcome. Laser-treated vs. cryotherapy treated threshold eyes had more favorable outcome. Geometric visual acuity: Laser 20/33 / Cryotherapy 20/133 / P 0.03 Range: (20/20-20/70) / (20/25 to phthisis) Mean refractive error(D): -6.5 / -8.25 / 0.27 Conclude: Laser therapy for threshold ROP may have long-term visual function advantages over cryotherapy.	Small numbers for randomized comparison. It is not clear how similar were the groups in terms of original threshold ROP (zone I vs. II)	No data on funding source

Evidence Table 8. Studies of Treatment Effects for LBW Infants with Retinopathy of Prematurity (ROP)
Part III

Author, Year	Associations found							Potential Biases	Comments
		Predictors/Conditions	N	Outcome Category	Outcome of Interest/ Instruments used	% with Outcome	Methods of Correlation		
O'Connor 2002 21635822	**Full term**	Control	169	Visual function	Distance Acuity (Left eye)	-0.08 (-0.1,0.01)			
	BW <1701 all	Premature cohort	254	Visual function	Distance Acuity (Left eye)	0.0 (-0.08,0.1)			
	No ROP	Premature cohort	126	Visual function	Distance Acuity (Left eye)	0.0(-0.08,0.04)			
	Stage 3 or 4 ROP	Premature cohort	7	Visual function	Distance Acuity (Left eye)	0.34(0.21,0.605)			
	Full term	Control	169	Visual function	Binocular Distance Acuity	Normal 93% ≥Moderately reduced 0%	P<0.001 between control vs. premature cohort		
	BW <1701 all	Premature cohort	254	Visual function	Binocular Distance Acuity	Normal 76% ≥Moderately Reduced 3.5%			

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcome

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Als 1994 94358983 (CNS+ Pulmonary)	Location: US Years of Birth: ND Median GA (range), wk: Experiment: 27.1±1.6 Control: 26.5±1.4 Median BW (range), g: Experiment: 827±173 Control: : 862±145 Male: Experiment: 45% Control: 61% Race: Black Experiment: 40% Control: 17% SES I, II/III/IV, and V: Experiment: 45%, 20%, 35% Control: 56%, 17%, 27% Enrolled: 43 Evaluated: 38 Number of sites: 1	BW < 1250 g GA < 30 weeks and more than 24 weeks of estimated GA at birth Mechanical ventilation starting within the first 3 hrs after birth and lasting longer than 24 hrs in the first 48 hrs Alive at 48 hrs Absence of chromosomal or other major genetic anomalies, congenital infections, and known fetal exposure to drugs of addiction Singleton At least one family member with some English-language facility Telephone access Living within the greater Boston area	ND	Experiment: VLBW infants participated in individualized developmental care (20) Controls: VLBW infants received standard care (18)	Randomized controlled trial (2 weeks and 9 months)
Chye 1995 95314864	Location: Australia Years of Birth: 1989 to 1990 Mean GA (range), wk: Cases: 28±1.58 Controls: 28.63±1.26 Mean BW (range), g: Cases: 1055± 234 Controls: 1077±215 Male: 56% Race: ND Enrolled: 80 Evaluated: 78 (78 controls) Number of sites: 1	Cases: 26-33 week GA infants with BPD and discharged home Controls: 26-32 week GA infants without BPD admitted to the hospital within 1 year of the cases, matched for BW with the cases in broad categories (<1000 g, 1000-1499 g and =1500 g)	Cases: Trisomy 21 (2)	Cases: Preterm infants with BDP (78) Sample 2: Preterm infants without BPD (78) Subgroups of cases at 12 months corrected age follow-up: Sample 1: BPD no Home O_2 (58) Sample 2: BPD with Home O_2 (20)	Case-control study

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcome

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Kraybill 1995 95264242	Location: USA Years of Birth: 1986-1989 Mean GA: (F/up at 1 year) Sample 1: 28.2 ±1.9 Sample 2: 28.1 ±2.0 Mean BW: Sample 1: 1022 ±177 Sample 2: 1028 ±184 Male: Sample 1: 51% Sample 2: 52% Race: Sample 1: White: 21%, Black: 53%, Hispanic: 23%, Other; 4% Sample 2: White: 34%, Black: 42%, Hispanic: 22%, Other: 2% Enrolled: 323 (survivors at 1 yr) Evaluated: 258 (at 1 yr f/up) Mean GA (F/up at 2 years of age) Sample 1: 28.3 ±1.8 Sample 2: 28.1 ±1.8 Mean BW: Sample 1: 1043 ±165 Sample 2: 1005 ±184 Male: Sample 1: 49% Sample 2: 43% Race: Sample 1: White: 35%, Black: 60%, Other:5% Sample 2: White: 43%, Black: 54%, Other: 3% Enrolled: 136 (survivors at 2 yrs) Evaluated: 118 Number of sites: 2	Premature VLBW: 700-1350 g (Detailed description available in another article)	ND	At 1 yr f/up Sample 1: Synthetic Surfactant at Birth via ET tube: 5 ml/kg (136) Sample 2: Air placebo via ET tube at birth (122) At 2 yr F/up: Sample 1: Synthetic surfactant at birth (57) Sample 2: Air placbo (61)	Randomized placebo-controlled double blind trial (at 1 year and at 2 years CA)

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcome

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Santuz 1995 96023205	Location: Italy Years of Birth: 1981-1987 Mean GA (range), wk: Cases: 30±2 (27-32) Controls: 39±1 (37-40) Mean BW (range), g: Cases: 1400±335 (890-1900) Controls: 3335±418 (2800-4100) Male: Cases: 75% Controls: 69% Race: ND Enrolled: 12 (16 controls) Evaluated: 12 (16) Number of sites: 1	Cases: Premature, RDS with mechanical vent > 7 days; met criteria for BPD; agreed to cooperate Control: healthy term school children matched for age, height, weight, habitual level of physical activity	Cerebral palsy; too young to cooperate	Cases: Preterm infants with BPD (12) Controls: Healthy term infants (16)	Case-control study (6-12 years)
Iles 1997 97280982	Location: UK Years of Birth: ND Mean GA (range), wk: ND Median BW (range), g: 900 (589-1891) Male: ND Race: ND Enrolled: 40 Evaluated: 33 Number of sites: 1	Premature birth Continuous supplemental O2 for 28 days after birth	Refused consent Returned to referring hospital	Premature infants with CLD (33)	Prospective cohort
Cheung 1998 99059896	Location: Canada Years of Birth: 12/93-10/97 Mean GA (range), wk: 25 (24-30) Median BW (range), g: 860 (340-1460) Male: 67% Race: ND Enrolled: 24 Evaluated: 10 Number of sites: 1	VLBW survivors, BW < 1500 g, requiring inhaled nitrous oxide (INO) (continues to be hypoxenic at >90% O_2 and MAP 15 ± 2)	Mosaic trisomy 18 Potter's syndrome survived to 1 year of chronological age	VLBW infants treated with INO (10)	Prospective cohort

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcome

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Gross 1998 98375435	Location: US Years of Birth: 1985-1986 Mean GA (range), wk: Sample 1: 28.2±2.1 Sample 2: 28.4±2.0 Controls: 40±1.1 Mean BW (range), g: Sample 1: 1173±345 Sample 2: 1179±354 Controls: 3565±427 Male: Sample 1: 53% Sample 2: 51% Controls: 57% Race: White Sample 1: 86% Sample 2: 85% Controls: 89% Enrolled: 133 (125 controls) Evaluated: 96 (108) Number of sites: 1	All live-born babies 24-31 wk gestation cared for at Crouse Memorial Hospital, survived to discharge Controls: FT AGA, 38-42 wk GA. PT matched to FT for sex, mat. Race, mat. Educa. and marital status (sociodemographic factors).	ND	(Sample 1&2): Preterm infants (96) Sample 1: Preterm infants with BPD (43) Sample 2: Preterm infants without BPD (53) Controls: Full term infants (108)	Prospective cohort (7 years) Cases: 8 died after discharge because of complications of chronic lung disease (2), pneumonia (2), nonrespiratory conditions (4), lost to follow-up (6), and neurodevelopmental delays (23) Controls: lost to follow-up (12), neurodevelopmental delays (5)
Kurkinen-Raty 1998 98387235 (All+Lung) ***sample from the same big population as 20284814**	Location: Finland Years of Birth: 1990-1996 Mean GA (range), wk: Cases: 28.2 (23.8- 37.2) Controls: 28.4 (22.9-36.9) Mean BW (range), g: Cases: 1138.3±434 Controls: 1272.4±547.2 Male: ND Race: ND Enrolled: 78 (78 controls) Evaluated: 78 (78) Number of sites: 1	Preterm PROM between 17-30 weeks gestation; singleton; delivered > 2 hr after rupture Controls: preterm no PROM; spontaneous preterm delivery matched for GA and year of delivery.	Rupture unconfirmed or transient	Sample 2: Preterm rupture (78) Sample 2: Preterm delivery no rupture (78)	Retrospective cohort

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcome

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Subhedar 1999 20257096	Location: UK Years of Birth: 6/1995-5/1999 Mean GA (range), wk: Sample 1: 28 (24-34) Sample 2: 30 (26-34) Mean BW (range), g: Sample 1: 1055 (510-2310) Sample 2: 1420 (840-2150) Male: Sample 1: 52% Sample 2: 52% Race: ND Enrolled: 98 Evaluated: 98 Number of sites: 1	Sample 1: Preterm infants with CLD Sample 2: Preterm infants without CLD received mechanical ventilation <24 hours + 02< 72 hours	ND	Sample 1: Preterm infants with CLD (54) Sample 2: Healthy preterm infants (44)	Prospective cohort
Kurkinen-Raty 2000 20284814 ***sample from the same big population as 98197235**	Location: Finland Years of Birth: 1990-1997 Mean GA (range), wk: Cases: 30.5±2.1 Controls: 30.4±2.1 Mean BW (range), g: Cases: 1294±469 Controls: 1605±427 Male: ND Race: ND Enrolled: 103 (103 controls) Evaluated: 103 (103) Number of sites: 1	Cesarean delivered singleton, GA 24-33 weeks Controls: spontaneously delivered singleton after regular contractions and/or preterm rupture of the membranes no more than 24 hrs before. The mothers were matched one-to-one by gestational age at delivery plu7s or mines 1 week.	ND	Sample 1: Indicated preterm I.e. preterm birth 'indicated' for maternal/fetal reasons (103) Sample 2: Spontaneous preterm delivery due to preterm labor (103)	Retrospective cohort

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcome

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Brooks 2001 21153125	Location: US Years of Birth: 1988 Mean GA (range), wk: ND Mean BW (range), g: ND Male: ND Race: ND Enrolled: 8071 Evaluated: 8071 Number of sites: 1	< 4 year old selected from randomized, systematic population based sample, weighted to be nationally representative of sampling of African-American and LBW infants who had initial (1988) and follow-up (1991) surveys and asthma reports	ND	VLBW infants (<1500g), MLBW (1500-2499g); NBW (=2500) infants from NMIHS population (8071)	Prospective cohort Follow-up 3 years 1988-1991
Doyle 2001 21064379 ***overlapped sample with Ford, 2000 20380862 in growth table**	Location: Australia Years of Birth: 1/1977 to 3/1982 Mean GA (range), wk: Sample 1: 27.5 ±2.3 Sample 2: 29.6 ±1.5 Controls: 39.9 ±1.0 Mean BW (range), g: Sample 1: 859±100 Sample 2: 1248±145 Controls: 3420±427 Male: Sample 1: 45% Sample 2: 54% Controls: 62% Race: ND Enrolled: 210 (60 controls) Evaluated: 180 (42 controls) Number of sites: 1	Sample 1: 86 consecutive ELBW survivors (BW 500-999g) born during the 63 months from 1/1/1977 Sample 2: 124 consecutive ELBW survivors (BW 1000-1500g) born during the 18 months from 1/10/1980 Control: 60 randomly selected term infants with BW>2499g born within the Royal Women's Hospital during the last 6 months of the recruitment phase	ND	Sample 1: Preterm ELBW infants, BW 500-999g (78) Sample 2: Preterm ELBW infants, BW 1000-1500g (102) Control: Term infants, BW >2499g (42)	Prospective cohort (14 years)

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Als 1994 94358983	Other: Participation in individualized developmental care staffing by specially educated nurses	The psychologist and clinical nurse specialist provided ongoing support for the care teams and parents of the infants in the experimental group in jointly planning and implementing individually supportive care and environments.	**CNS:** Neurodevelopmental: Cognitive delay **Pulmonary:** BPD severity	Baley Scale of Infant Development at 9 months of age Assessed by double-blind review of cranial US scans by a consultant senior radiologist
Chye 1995 95314864	**Bronchopulmonary dysplasia** BPD with Home O_2 BPD without Home O_2	Diagnoses of BPD was based on Bancalari's BPD definition Home oxygen therapy program – infants who were well, feeding satisfactorily and gaining weight, but were unable to maintain adequate oxygenation (93-97% saturation) in room air, and were therefore discharged from hospital under the home oxygen therapy	**Growth** Re-hospitalization	Growth was based on sex-specific National Center of Health Statistics growth chart

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Kraybill 1995 95264242	**General:** Surfactant (single dose 5 ml/kg given via ET tube at birth)	As soon as after birth, infants were treated either with 5 ml/kg of surfactant or air placebo, via ET tube.	At 1 yr assessment (NCMH and HCHD cohort): **General:** Overall survival **Pulmonary:** Need for O2 via Nasal canula Need for O2 via CPAP CLD At 2 yr assessment (NCMH cohort) **General:** Overall survival Hospitalization for respiratory illness **Pulmonary:** Bronchodilator regular use Tracheostomy At 1 and 2 yr assessment: **Growth:** Height for age Weight for age HC for age Mean MDI score MDI scores < 2 SDs Mean PSI score PDI scores < 2 SDs Severity of impairments Types of Impairments Any surgery (between 28 ds-1 yr or 1yr to 2 yr) Assessment between 28 ds-12mo: **Ophthalmology:** ROP (No ROP, Mild/moderate, Severe) Tx for ROP(surgery or cryotherapy) ROP presence at latest exam Severe ROP	No further specifications given, except for the followings: Oxygen via Nasal canula : providing alveolar O2 concentrations of : 26%-40%, based on NC flow and NC O2 concentration Bayley Scale of Infant Development: • MDI= Mental Development Index Score • PDI: Psychomotor Development Index Score ROP : (not further definitions) • No ROP, • Mild/moderate • Severe CP (no further definitions) • Mild • Moderate/Severe Severity of impairments: • Severe • Mild/Moderate Types of impairments: • MDI<69 • MDI: 69-84 • Moderate/severe CP • Mild CP • Bilateral sensorineural deafness • Deafness not requiring amplification • Bilateral blindness • Visual defect (1 yr and 2 yr CA)

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Santuz 1995 96023205	General Predictor: GA Cardiovascular 1) Chronic Lung Diseases 2) Other: duration of supplemental oxygen	Chronic Lung Disease defined as oxygen dependency for at least 28 days and beyond 36 postmenstrual weeks in association with an abnormal chest radiograph.	Other Outcomes: Cardiovascular: pulmonary hypertension	Measured as AT/RVET ratio = Doppler derived acceleration time to right ventricular ejection time ratio
Iles 1997 97280982	*Cardiovascular or Pulmonary Predictors:* Bronchopulmonary dysplasia *Other Predictors:* ECG with RVH	$DaAO_2$ in 50% O_2 $PaCO_2$ PFT testing to determining V_{max} FRC	**Pulmonary:** Requirement for supplemental O_2 at one year CA; alternately phrased by authors as SaO_2 < 90% in RA **Other outcomes**: Hospital readmission	ND
Cheung 1998 99059896	Cardiovascular or Pulmonary Predictors: Inhaled nitric oxide (INO)	ND	**Pulmonary:** BPD or CLD (with or without meds) Aspiration pneumonia	PDI + MDI of Bayley Scales of Infant Developmental Index were used. "Neurodevelopmental" outcomes: Disability: one of more of: 1. CP (all types or severity) 2. Legal blindness (corrected visual acuity of the better eye <20/200 3. Hearing loss (sensorineural hearing loss of >30 dB in the better ear) 4. Severe mental retardation (MDI >3 SD below the mean) Delay: does not have disability and either MDI or PDI was >2 SD below the mean. Normal: free of disability or delay and MDI and PDI were within 2 SD of the mean.

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Gregoire 1998 95264241	Cardiovascular/Pulmonary: 1) Chronic Lung Disease 2) Bronchopulmonary dysplasia Compared O_2 dependence at 28 days with O_2 dependence at 36 wk	ND	**CNS:** Cerebral palsy Motor and cognitive delay **Audiology**: Hearing Disorders→ Free field audiograms **Pulmonary:** Respiratory readmissions PICU admissions **Growth:** Weight, height, head circumference **Other:** Health Outcomes	Giffith's Mental Development Scales Neurologic examinations
Gross 1998 98375435	General: GA Cardiovascular: Bronchopulmonary dysplasia @ 30 wk Other: social data, health data	PT 24-31 wk GA BPD if infants were dependent on supplemental oxygen @ 35 wk PMA	**Pulmonary:** Respiratory symptoms (wheeze, chronic cough, chest congestion) Restriction in activity, Use of respiratory medicines, 7-year pulmonary function studies Bronchodilator responsivness **Other:** Re-hospitalization Metabolic measures	Lung function testing was performed on SensorMedics 2200 (SensorMedics, Anaheim, Calif) by investigators blinded to children's GA and medical histories
Kurkinen-Raty 1998 98197235	General : PROM	Diagnose was through clinical assessment or with the use of a PROM-test, which detects insulin growth factor binding protein-1 in the cervico-vaginal secretions, or with the use of a nitrazine test.	**CNS:** Motor delay Cerebral delay **Ophthalmology**: Visual Blindness **Audiology:** Hearing disorders **Pulmonary**: Chronic lung disease **Growth:** weight percent **Other:** Days of re-hospitalization Steroid therapy at follow-up	Neurologic exams Diagnosis of CLD was made if infants required oxygen, continuous bronchodilator, or steroid tx because of respiratory signs and symptoms. Diagnoses of RDS were made based on need for respiratory support, radiologic findings, and clinical assessments

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Subhedar 1999 20257096	Cardiovascular/Pulmonary: Chronic lung disease	CLD was defined as oxygen dependency for at least 28 days and beyond 36 PMA in association with an abnormal chest radiograph	**Pulmonary:** 1) Pulmonary function-forced vital capacity 2) Minor ventilation forced expiratory volume, forced expiratory flow Other: Heat rate during exercise	Measures OR aerobic power: a) maximum O2 consumption b) max O2 consumption at anaerobic threshold C) running time
Kurkinen-Raty 2000 20284814	General predictors: Birth weight GA Antenatal steroids Cord pH Bronchopulmonary dysphasia (BPD) Other predictors: Indicated preterm delivery Spontaneous preterm delivery	BPD diagnoses were based on radiologic finding	**CNS:** Motor delay Cerebral palsy **Ophthalmology** Visual impair ment **Audiology** Hearing disorder **Pulmonary** Chronic lung disease (CLD) at 1 year **Growth:** Wt, Ht, HC	Motor delay = abnormalities of tone or reflexes but functionally normal or borderline CP = spastic diplegia or hemiplegia or spastictetraplegia Diagnosis of CLD was made if infants required oxygen, continuous bronchodilator, or steroid tx because of respiratory signs and symptoms.
Brooks 2001 21153125	General: Birth weight Sex Other: SEC factors (mat age, race, education, SEC status, mat wt gain, mat smoking, poverty status variable) Prenatal history Developmental outcomes	Predictors self-explanatory. Poverty variable based on family income and number of household members, categorized by standard national poverty levels.	**Pulmonary:** M.D. diagnosed asthma in 1st 3 years of life	Diagnosis of asthma based on response of parent to question, "Have you been told by a MD/ RN/other health provider that your child has asthma?"
Doyle 2001 21064379 ***overlapped sample with 20380862**	General: Birth weight Cardiovascular/Pulmonary: Bronchopulmonary	ND	**Pulmonary:** 1) Asthma 2) Lung function testing 3) readmission to hospital for asthma or pneumonia **Growth:** height **Other**: hospital readmission	Lung function testing, Jaeger Bodyscreen II-Bodybox (Jaeger, Germany), with Masterlab (ML3) software

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcomes
Part III

Author, Year	Associations found				Potential Biases	Comments
Als 1994 94358983	Studied effect of an individualized developmental care plan on Bayley score at 9 months age and occurrence and severity of BPD.				Small number of babies studied Only one NICU Only one neurodevelopmental assessment at 9 months of age Reported timing of IVH different from many other studies High potential for contamination	Study was government funded
		Experimental group	Controls	P value		
	N	20	18			
	Bayley MDI	118.30 (17.35)	94.38 (23.31)	< 0.001		
	Bayley PDI	100.6 (20.19)	83.56 (17.97)	< 0.01		
	No BPD	2/20	3/18			
	Mild BPD	13/20	7/18			
	Moderate BPD	5/20	2/18			
	Severe BPD	0	6/18	0.03		

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Chye 1995 95314864	Rehospitalization rate (overall) BPD (78) 58% Control (75) 35% RR 1.7 (1.2-2.4) Rehospitalization for respiratory illness BPD (78) 39% Control (75) 20% RR 1.9 (1.1- 3.2) Rehospitalization for poor growth BPD (78) 14% Control (75) 1% RR=1.4 (1.7-82) Rehospitalization for failure to thrive BPD on home O_2 (20) 30% Control no home O_2 (58) 9% RR=3.3 (1.2-8.9) **Growth (wt in kg) :** NS diff between BPD and control BPD M 9.08 F 8.4 Control M 9.37 F 8.82 **Growth (Ht in cm):** NS diff BPD M 73.0 F 72.1 Control M 74.4 F 72.6 **Growth (HC in cm):** NS diff BPD M 46.7 F 46.0 Control M 47.0 F 454. There was a significant increase in **any** rehospitalization in 1st year of life in preterm infants with BPD vs. preterm infants with no BPD. There was a significant increase (2-fold) in rehospitalization for **respiratory illness** in the 1st year of life in preterm infants with BPD vs. preterm infants with no BPD. BPD infants with Home O2 (N=20) had ~3 fold increased re-hospitalization for failure to thrive. Growth failure was common in both preterm groups (i.e. in infants with no BPD and with BPD <10% in weight at 1 yr age). Re-hospitalization was high in both preterm groups (with and without BPD).	(None)	Study was privately funded

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Kraybill 1995 95264242	Single dose Surfactant tx at birth was not associated with the physical and neurodevelopmental status of VLBW premature infants at 1 yr of corrected age Placebo group vs Surfactant group, at 1 yr of age: 1. Overall survival at 1 yr: 2. Oxygen via NC 3. Oxygen via CPAP: 4. CLD 5. Distribution of pts in both groups across different percentiles: Ht/age, Weight/age and HC/age: were not s/s different across the two groups. 6. Mean MDI score: 7. MDI scores< 2SDs 8. Mean PDI score: 9. PDI scores < 2 SDs: 10. No impairment: 11. Impairment present (total) 12. Severe impairment: 13. Mild/Moderate impairment: 14. Types of impairment: MDI<69: MDI: 69-84: Moderate/severe CP: Mild CP: Bilateral sensorineural deafness: Deafness not requiring amplification Bilateral blindness: Visual defect: Assessment from 28ds-12 mo: • No ROP: • Present ROP overall: • Mild/Moderate ROP: • Severe ROP: • Treatment for ROP overall: Surgery: Cryotherapy: In the NCMH cohort there was no difference in impairments, the severity of impairments and the types of impairments at the 1yr of age assessment		

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Santuz 1995 96023205	Forced vital capacity (FVC): BPD: (N=12) 87±10 Without BPD: (N=16) 96±8 <0.05 Forced expiratory volume(1 sec)(FEV1): BPD: 83±12 Without BPD: 100±8 <0.01 FEF 25-75 (forced expiratory flow between 15-7520 vc): BPD: 77±30 Without BPD: 110±14 <0.01 Oxygen consumption (ml/?/?): BPD: 25.2±10.3 Without BPD: 37.1±10.4 <0.01 Running time (minutes): BPD: 6.1±1.3 Without BPD: 7.9±2.6 <0.05 Minute ventilation: BPD: 20±9.4 Without BPD: 30.7±9 <0.01 Max heat rate during exercise: BPD: 192±7.9 Without BPD: 194±8 Not significant Running time: BPD: 6.1±1.3 Without BPD: 7.9±2.6 P <0.05	Small study Far from comprehensive; likely substantial section bias Compares prematures with BPD to term infants without BPO; unclear if results are due to BPD or prematurity	No data on funding source

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Iles 1997 97280982	Study of chronic lung disease (CLD) leading to a persistent requirement for supplemental oxygen at one year of age. N % requiring oxygen at one year age Supplemental O2 at discharge 6 50% RVH on ECG 3 100% Alveolar arterial oxygen gradient > 29 kPa in 50% hood oxygen at 35 to 40 weeks PCA predicted need for supplemental oxygen at one year with sensitivity 0.85 and specificity 0.88. PaCO2 greater than 7 kPa at 35 to 40 weeks PCA predicted supplemental oxygen requirement at one year with sensitivity 0.78 and specificity 0.88.	Small number of infants No information regarding early neonatal course No control groups of preterms without CLD	Study was privately funded
Cheung 1998 99059896	Mean MDI 81 ± 21, PDI 64 ± 22 Normal development 31% Neurodevelopmental delay 20% Disabled 50% Severe mental retardation 10% Spastic diplegic CP 30% Hemiplegic CP 10% <3rd %ile for weight 20% <3rd%ile for height 40% <3rd%ile HC 30% BPD 80% Need bronchodilators for CLD 10% Recurrent wheezing but did not need meds 40% Grade 4 IVH 20% Grade 3 IVH 20% VP shunt 30% PVL 10% Sensorineural hearing loss 10%	Very small sample size Descriptive study with no control group for comparison	No data on funding source

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Gross 1998 98375435	Rehospitalization during 1st 2 years: PT with BPD 23/43 (53%) PT without BPD 14/53 (26%) FT 3/108 (3%) Respiratory symptoms in PT with BPD were greater than symptoms in PT without BPD, and both were greater than FT group Pulmonary function Tests: Multiple tests revealed significantly worse PFTs in PT with BPD at rest and after exercise compared to either PT without BPD or FT group. Exercise results: No difference in baseline HR, VO2, RQ, Max VO2, Max RQ, endurance among groups Asthma: PT with BPD 20/43 (47%) PT without BPD 13/53 (25%) FT 23/108 (21%) PT with BPD vs. FT: P<0.001 School age children who were former preterm infants with BPD demonstrated abnormal pulmonary function at 7 years age in contrast to school age children who were preterm infants without BPD or FT AGA control. The children who were preterm infants without BPD had similar pulmonary function as children who were FT AGA controls.	(None)	No data on funding source

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Kurkinen-Raty 1998 98387235	Retrospective controlled cohort study of early PROM between 17 and 30 weeks of gestation. Assements at one year corrected age. N = 55 for early PROM and 56 for control. Outcome / Early PROM / Control / OR (CI) Cerebral palsy 18% 16% 1.2 (0.4, 3.1) Delayed motor Development 9% 16% 0.5 (0.2, 1.7) Visual disability 4% 4% 1.0 (0.1, 7.5) Hearing loss 7% 9% 0.8 (0.2, 3.2) Good nuerosensory development 67% 61% 1.2 (0.6, 2.2) Early PROM seems to be a major obstetric and neonatal problem with pulmonary ramifications extending beyond the neonatal period. However, most of these infants can be saved.	(None)	No data on funding source
Subhedar 1999 20257096	AT/RVET ratio much lower in CLD group p< 0.01. Pulmonary arterial pressure remains persistently elevated in CLD infants until the end of first year of life.	Does not state whether the Doppler evaluators were blinded to the groups	Study was private funded

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Kurkinen-Raty 2000 20284814	**CLD at 1 year age:** Indicated PT delivery: (81) 12/81 (15%) Spontaneous PT delivery: (94) 3/94 (3%) RR 4.6 (1.4, 1.6) **Growth:** Indicated PT delivery: (81) Spontaneous PT delivery: (94) Weight RR =0.03 (-5.3, 0.3) L RR = 0.002 HC RR = 0.03 **CP:** Indicated PT delivery: (81) 5/81 (6%) Spontaneous PT delivery: (94) 10/94 (11%) RR=0.6 (0.25-1.6) **Delayed motor:** Indicated PT delivery: (81) 8/81 (6%) Spontaneous PT delivery: (94) 8/94 (9%) RR 1.2 (0.5-3.0) **Visual disability:** Indicated PT delivery: (81) Spontaneous PT delivery: (94) RR =1.9 (0.5, 7.8) **Hearing loss:** Indicated PT delivery: (81) Spontaneous PT delivery: (94) RR =1.9 (0.5, 7.8) 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 yr age. More infants in 'indicated' group were SGA and were significantly smaller than control group at 1 yr in Wt, HT, and HC. There was no difference between groups in neurosensory outcomes.	Outcome not well-defined Difficult to know if lack of difference between groups is due to sample size or event rate.	No data on funding source

Evidence Table 9. Studies Evaluating Association of LBW and Pulmonary Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Brooks 2001 21153125	Diagnosis asthma by age 3 years BW ≥ 2500 gm 6.7% BW≥1500-2499gm 10.9% OR=1.4 (1.1-1.8) BW < 1500 (VLBW) 21.9% OR=2.9 (2.3-3.6) African-American 12% OR=1.9 (1.6-2.4) VLBW/African-American OR 2.5 (2.0-3.3) VLBW/white OR=3.1 9 (2.2-4.3) Chronic lung disease (8058) 20.4% OR 3.4 (2.4-4.8) 68% attributable risk for asthma in VLBW children was due to birth weight.	Retrospective classification of BPD may have been limited compared to prospective classification. Potential for selection bias a. identifying asthma children based on parental report of physician-diagnosed asthma. (Evidence of high specificity and PPV) b. defining asthma may vary by physician practice	Study was government funded Objective of study was to estimate the independent contribution of BW to asthma prevalence among children <4 years age. This study found a strong, independent association between low birth weight and asthma.
Doyle 2001 216464379 ***overlapped sample with 20380862**	Respiratory health and lung function in these preterm children <1501g were mostly normal and comparable with normal control term infants at 14 years	(None)	Study was privately funded

Evidence Table 10. Studies Evaluating Association of LBW and Bone and Growth Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Forslund 1992 93044002	Location: Sweden Years of Birth: ND Median GA (range), wk: ND Mean BW (range), g: ND Male: ND Race: ND Enrolled: ND Evaluated: 41 (24 controls) Number of sites: ND	ND	ND	Cases: Preterms (41) Controls: Term infants (24)	Unclear (the study design was described in detail in previous papers)
Chye 1995 95314864	Location: Australia Years of Birth: 1989 to 1990 Mean GA (range), wk: Cases: 28±1.58 Controls: 28.63±1.26 Mean BW (range), g: Cases: 1055± 234 Controls: 1077±215 Male: 56% Race: ND Enrolled: 80 Evaluated: 78 (78 controls) Number of sites: 1	Cases: 26-33 week GA infants with BPD and discharged home Controls: 26-32 week GA infants without BPD admitted to the hospital within 1 year of the cases, matched for BW with the cases in broad categories (<1000 g, 1000-1499 g and =1500 g)	Cases: Trisomy 21 (2)	Cases: Preterm infants with BDP (78) Sample 2: Preterm infants without BPD (78) Subgroups of cases at 12 months corrected age follow-up: Sample 1: BPD no Home O_2 (58) Sample 2: BPD with Home O_2 (20)	Case-control study
DeReignier 1997 98041177	Location: Netherlands Years of Birth: 1/1/1987-12/31-1991 Median GA (range), wk: 27.5 Mean BW (range), g: 1015 Male: 48% Race: 38% Black Enrolled: 678 Evaluated: 174 Number of sites: 1	VLBW infants , BW < 1500 g, survived until discharge Matched sever CLD and no CLD infants to mild CLD infants for BW, race, and sex.	Condition independent of CLD known to adversely affect neurosensory status, development, growth; significant congenital anomalies; congenital viral infections; SGA; NEC requiring enterostomy	Matched VLBW infants (89): No CLD (58) Mild CLD (58) Severe CLD (58)	Retrospective cohort (followed until 1 year adjusted age)

Evidence Table 10. Studies Evaluating Association of LBW and Bone and Growth Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Gosch 1997 97379896	Location: US Years of Birth: 1989 to 1994 Mean GA (range), wk: Cases: 27.6 (26-29) Controls: 39 (36-40) Mean BW (range), g: Cases: 880 Controls: 3466 Male: 50% Race: ND Enrolled: 5 (5 controls) Evaluated: 5 (5) Number of sites: 1	Participants in a early intervention and family care for blind infants and preschoolers Blind children	ND	Cases: Blind children born preterm (5) Controls: Blind children born full term (5)	Retrospective cohort (24, 36, 48, and 58 months)
Ladd 1998 98357452	Location: US Years of Birth: 1980-1995 Mean GA (range), wk: 30 (23-42) Mean BW (range), g: 1500 (272-4840) Male: 53% Race: ND Enrolled: 249 Evaluated: 249 Number of sites: 1	249 babies with NEC who had their initial surgical care at the James Whitcomb Riley Hospital for Children Indiana University Medical Center campus, with the diagnosis of NEC from 1/1/1908-12/31/1995 were included in the study	Infants with focal, isolated perforations of the ileum were excluded	Infants with NEC (249)	Retrospective cohort (16 years)

Evidence Table 10. Studies Evaluating Association of LBW and Bone and Growth Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Wang 1998 98244087	Location: Canada Years of Birth: 1/1977 to 5/1992 Mean GA (range), wk: 27.7±2.3 Mean BW (range), g: 954.6±185.9 Male: 48% Race: Caucasian 88.5% SES: low SES category (Blishen index=40) 47.2% Enrolled: 1007 Evaluated: 514 Number of sites: 1	VLBW infants, BW<1250g, survived to NICU D/C	Missing more than one measurement	VLBW infants (514)	Prospective cohort (36 months)
Connors 1999 99250892	Location: Australia Years of Birth: 1/1987 to 12/1992 Mean GA (range), wk: 27±2.2 Mean BW (range), g: 822.8 ±125 Male: 45% Race: ND Enrolled: 226 Evaluated: 198 Number of sites: 1	ELBW survived infants, BW <1000 g	Died by 2 years corrected age (1) Lost to follow-up (12) Transferred interstate and limited information was available (4)	ELBW infants (198): Sample 1: ELBW with low perinatal risk factors (128) Sample 2: ELBW with high perinatal risk factors (70)	Prospective cohort (2 year CA)

Evidence Table 10. Studies Evaluating Association of LBW and Bone and Growth Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
French 1999 99115141 (CNS + Growth+ All)	Location: Australia Years of Birth: 1990-1992 Median GA (range), wk: Sample 1: 30 (26-32) Sample 2: 29 (27-31) Sample 3: 30 (28.5-31.5) Sample 4: 31 (29-32) Mean BW (range), g: Sample 1: 1435 (905-1810) Sample 2: 1345 (1000-1735) Sample 3: 1517.5 (1210-1660) Sample 4: 1455 (1080-1715) Male: total 57% Race: ND Enrolled: 652 Evaluated: 477 Number of sites: 1	Singleton live-born infants GA <33 weeks	ND	Sample 1: Antenatal steroids x 0 course (311) Sample 2: Antenatal steroids x 1 course (123) Sample 3: Antenatal steroids x 2 courses (20) Sample 4: Antenatal steroids x > 3 courses (23)	Prospective cohort (3 years)
Ford 2000 20380862 ***overlapped sample with Doyle, 2001 21064379 in Lung table**	Location: Australia Years of Birth: 1/1977 to 3/1982 Mean GA (range), wk: Sample 1: 27.5 ±2.3 Sample 2: 29.6 ±1.5 Controls: 39.9 ±1.0 Mean BW (range), g: Sample 1: 859±100 Sample 2: 1248±145 Controls: 3420±427 Male: 56% Race: ND Enrolled: 206 (60 controls) Evaluated: 179 (42 controls) Number of sites: 1	Cases: Preterm ELBW infants (<1500g) who survived to discharge Control: Full term NBW (BW>2499g) infants group who survived to discharge	Children with CP at age 14 years Lost to follow-up	At 14-year follow-up: Cases (Sample 1&2): Preterm ELBW infants (179) Sample 1: Preterm infants, BW<1000g (79) Sample 2: Preterm infants, BW 1000-1499g (100) Control: Full term NBW infants (42)	Prospective cohort (14 years)

Evidence Table 10. Studies Evaluating Association of LBW and Bone and Growth Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Morley 2000 20167446	Location:UK Centers:5 Enrollment period: ND Age at assessement:7.5-8 yrs Trial 1: conducted in 3 centers Total enrolled in trial 1 and 2: N=926 infants with BW< 1850 g Long term f/up at 7.5-8 yrs of age: N=781 of 833 (94%) survivors	Premature BW< 1850 g Survivors of participants in the two RCTs with 2 parallel arms each (assessing effect of different neonatal diets of growth) Age 7.5-8 yrs	ND	GroupA: Prematures/ fed banked breast milk until weight 2000 g or discharge from the NICU N=207 Mean BW: 1397±297 Mean GA:31.1 % of SGA:30% Males: 53% Group B: Prematures/ preterm formula N=213 Mean BW:1387 ±278 Mean GA:31 % of SGAs:35% Males:52% (both groups included 2 parallel arms with or without supplementation with mother's own milk)	Two Randomized clinical trials Trial 1 and 2, with 2 parallel arms in each trial (The results for each trial are presented for the combination of the 2 parallel arms) Trial 1 had : Follow up At 9 mo At 18 mo At 7.5-8 yrs

Evidence Table 10. Studies Evaluating Association of LBW and Bone and Growth Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Avila-Diaz 2001 21334039	Location: Mexico Years of Birth: ND Mean GA (range), wk: Sample 1: 39±0.9 Sample 2: 30±2.6 Mean BW (range), g: Sample 1: 3195±323 Sample 2: 1294±167 Male: 51% Race: ND Enrolled: 82 Evaluated: 82 Number of sites: 1	Informed consent 48 full-term "healthy" infants and 34 pre-term infants who were predominantly breast-fed	ND	Sample 1: Full term infants (48) Sample 2: Preterm infants (34)	Prospective cohort (6 months)

Evidence Table 10. Studies Evaluating Association of LBW and Bone and Growth Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Forslund 1992 93044002	General: GA	Not given, resulted from previous papers of study with same group	**CNS:** Neurodevelopmental Motor delay **Growth** in height, weight and head circumference	Motor performance was tested by a physiotherapist: used TMI (test of motor impairment) Measurement of height Weight and head circumference by an experienced RN.
Chye 1995 95314864	Bronchopulmonary dysplasia BPD with Home O_2 BPD without Home O_2	Diagnoses of BPD was based on Bancalari' BPD definition Home oxygen therapy program – infants who were well, feeding satisfactorily and gaining weight, but were unable to maintain adequate oxygenation (93-97% saturation) in room air, and were therefore discharged from hospital under the home oxygen therapy	Growth Re-hospitalization	Growth was based on sex-specific National Center of Health Statistics growth chart
DeReignier 1997 98041177	General: GA Cardiovascular/Pulmonary: Chronic lung disease Gastrointestinal: Necrotizing "enterocolitis" Other: Osteomalcia = Socioeconomic status	No CLD- room air at 28 days Mild CLD- requiring 02 at 28 days but not at 36 wks PCA. Severe CLD- requiring 02 at 28 days and 36 wks PCA Not included in CLD if 02 used only for prevention of apnea	**CNS:** Motor delay Cerebral palsy Cognitive delay Mental retardation **Growth:** Weight Height Head circumference **Other** : Hospital readmissions	Motor and cognitive delay: corrected MDI or PDI scores were >2SD below mean (ie correct score <68) Mental retardation Growth: Weight, Length, Head circumference Development: Pediatrician & physical therapist agreed on presence of definitely abnormal position & posture from impaired neuromotor function Hospital readmission in 1st year

Evidence Table 10. Studies Evaluating Association of LBW and Bone and Growth Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Gosch 1997 97379896	Ophthalmology 1) Other: Blind ELBW 2) Other: blind Term (term control) Other Predictors 1) Nutrition/Growth-lead circumference(cm) 2) Other: days spent in hospital after delivery	Self-explanatory	**CNS:** Other: BDTB (Bielefeld developmental test for blind infants and pre-schoolers at age 18-48 months) **Growth:** Weight Height Head circumference Body mass index	The scales of BDTB including numbers of items and maximum scores listed on table 1
Ladd 1998 98357452	Gastrointestinal: 1) Short gut 2) Necrotizing "enterocolitis" 3) Presence of ileocecal valve 4) Length of bowel reserve	ND	Growth predictors: growth	ND
Wang 1998 98244087	BW	VLBW = 1250 g	Growth Weight Height	At the specified age and reference
Connors 1999 99250892	Birth weight (i.e. ELBW=BW <1 kg) Postnatal Nutrition Growth: <3%tile, 3-9%tile, ≥10%tile)	High perinatal risk: PVH>Grade 2 + ventriculomegaly, NEC, Home O2. Low perinatal risk: none of the above risk factors	CNS: CP Other adverse neurodevelopmental outcome Neurological Exam	Neurodevelopmental outcome assessed by Griffith's Developmental Scales, Motor outcome assessed by Neurosensory Motor Developmental Assessment [NMDA].
French 1999 99115141 (CNS + Growth+ All)	Other: Number of courses of antenatal steroids	ND	**CNS**: Neurodevelopmental CP **Growth:** Weight ratio Height ratio Head circumference ratio Disability	ND Weight, height, or HC compared to national standard "Any disability" = cerebral palsy, IQ< 85, deafness, or visual acuity worse than 6/60

Evidence Table 10. Studies Evaluating Association of LBW and Bone and Growth Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Ford 2000 20380862 ***overlapped sample with Doyle, 2001 21064379 in Lung table**	Birth weight	VLBW < 1500g (<1kg and 1-1.5 kg) vs Normal BW (>2.4 kg)	Growth outcome: Height Weight Head circumference Pubertal development	Growth scores and variables
Morley 2000 20167446	Trial 1: Type of diet in early neonatal period: • Banked donor breast milk vs Preterm formula (with or without supplementation with its mother's milk) Trial 2: • Preterm formula vs term formula (with or without supplementation with mother's milk)	Not further specified	Trial 1: Growth: Assessment at 9 and 18 months post-term: • Weight (kg) • Length (cm) • HC • Subscapular skinfold thickness • Body mass index Assessment at 7.5 –8 yrs: • All of the above • Also weight to hip ratio Trial 2: • Growth at 18 mo • Growth at 7.5-8 yrs	Not further specified
Avila-Diaz 2001 21334039	*General predictors:* 1) birth weight 2) preterm vs. full-term	ND	*Other outcomes:* 1) bone mineral contents (BMC) 2) bone area 3) changes in bone mineral content over time	BMC was measured monthly for full-term infants during the first 5 months of extrauterine life and bimonthly for pre-term infants during the first 6 months of extrauterine life

Evidence Table 10. Studies Evaluating Association of LBW and Bone and Growth Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Forslund 1992 93044002	Growth and motor performance assessed in preterm children at 8 years of life. • Differences for mean values for weight, height and head circumference not significant • Relationship exists between findings in TMI (test of motor impairment at 4 and 8 years) suggests possibility of identifying motor problems before school age.	A specific population in a certain are that has been studied before Lack of data regarding the population, stated birth weight significant but not listed anywhere	Study was privately funded Cannot generalize, general lack of data The population studied and the study design have been described in detail in previous paper

Evidence Table 10. Studies Evaluating Association of LBW and Bone and Growth Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Chye 1995 95314864	Rehospitalization rate (overall) BPD (78) 58% Control (75) 35% RR 1.7 (1.2-2.4) Rehospitalization for respiratory illness BPD (78) 39% Control (75) 20% RR 1.9 (1.1- 3.2) Rehospitalization for poor growth BPD (78) 14% Control (75) 1% RR=1.4 (1.7-82) Rehospitalization for failure to thrive BPD on home O_2 (20) 30% Control no home O_2 (58) 9% RR=3.3 (1.2-8.9) **Growth (wt in kg) :** NS diff between BPD and control BPD M 9.08 F 8.4 Control M 9.37 F 8.82 **Growth (Ht in cm):** NS diff BPD M 73.0 F 72.1 Control M 74.4 F 72.6 **Growth (HC in cm):** NS diff BPD M 46.7 F 46.0 Control M 47.0 F 454. There was a significant increase in **any** rehospitalization in 1st year of life in preterm infants with BPD vs. preterm infants with no BPD. There was a significant increase (2-fold) in rehospitalization for **respiratory illness** in the 1st year of life in preterm infants with BPD vs. preterm infants with no BPD. BPD infants with Home O2 (N=20) had ~3 fold increased re-hospitalization for failure to thrive. Growth failure was common in both preterm groups (i.e. in infants with no BPD and with BPD <10% in weight at 1 yr age). Re-hospitalization was high in both preterm groups (with and without BPD).	(None)	Study was privately funded

Evidence Table 10. Studies Evaluating Association of LBW and Bone and Growth Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
DeReignier 1997 98041177	Sensorineural Hearing Loss: CLD: No:0 Mild:0 Severe: 3 P<0.05 Low MDI (Bayley Scale): CLD: No: 0 Mild:4 Severe:5 P<0.05 Low PDI (Bayley Scale): CLD: No: 1 Mild:4 Severe:7 P<0.05 Cerebral Palsy No CLD vs Any CLD: Odds ratios: 6.4 95% CI: (1.05-139.8) Weight 2-Score: CLD: No: 2 score Severe: signify lower weight HC+ Length 2-Score: No, Mild, Severe: No significant difference	(None)	No data on funding source
Gosch 1997 97379896	Blind ELBW infants have developmental delay of 1.5 to 2 years that of term blind controls. **At 48 mos, ELBW blind vs Term blind BDTB scores:** Overall score: 169.4±62.4 vs 270.6±50.7, p <0.05 Neuromotor skills: not significant Social maturity: 42± 13.4, 67.4± 10.1, p < 0.05 Cognition: 16.8 ±22.5, 47.5 ±19.7, p< 0.05 Linguistic abilities: 11.2± 11.7, 29.2 ±12.5, p< 0.05 Socioemotional behavior:33±9.6, 44.8±6.3, NS Orientation and mobility: 35.6 ±10.7, 50.8± 5.9, p< 0.05 **ELBW blind infants had significantly lower weight,** height, head circumference and body-mass index than term blind infants.	Extremely small number of subjects only 5, so statistics not reliable Validity of BDTB scale still in question Does not state whether the evaluators were blinded to the groups or whether they were the same throughout the length of study.	No data on funding source

Evidence Table 10. Studies Evaluating Association of LBW and Bone and Growth Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Ladd 1998 98357452	Death rate of children with NEC was 49% 148 subjects with follow-up more than 2 years was evaluated for the impact of the ICV on severe growth retardation (<10 %tile) found that no association between length of bowel resected or status of the ICV, and sever growth retardation.	Extraordinary poor study Populations at follow-up times not described or compared Time of follow-up given only for 1 outcome Massive Bias Results not interpretable	No data on funding source
Wang 1998 98244087	More VLBW infants were classified as "subnormal growth" based on chronologic age vs. adjusted age through 36 months. The % of VLBW children with subnormal growth is therefore affected by adjustment for corrected age through 36 months and varies according to growth references (especially at younger ages 4-8 months). Regardless of adjusted or chronologic age or growth reference, the mean weight and mean height were significantly lower in VLBW (<1250 gm) than term infants at 4 through 36 months age. As infants approach 18 and 36 months age, the deviation from full term infants is less.	Large number of infants were not included in the analyses. They were slightly differed from the study sample in that they had higher BW and GA and less BPD and CP in follow-up	Study was privately funded
Connors 1999 99250892	Weight percentile was strongly associated with lower general growth quotient and lower motor abilities in ELBW infants. Low weight percentile at 2 year was related to adverse developmental outcome in ELBW infants at high perinatal risk or with neurological impairment. There was minimal association between postnatal low weight percentile and adverse neurodevelopmental outcome in ELBW infants who were at low perinatal risk and who had normal neurological exam. This study confirms strong association between low postnatal weight and adverse neurodevelopmental outcome. This association is stronger in infants with high perinatal risk factors and in infants with CNS impairment	(None)	No data on funding source
French 1999 99115141 (CNS + Growth+ All)	No significant association between antenatal corticosteroids and cerebral palsy, weight ratio at 3 years (median, IQR), height ratio median (IQR), head circumference ratio (median, IQR), and any disability (number, %)	Differential loss to follow-up not assessed Small number in severe group	No data on funding source

Evidence Table 10. Studies Evaluating Association of LBW and Bone and Growth Outcomes
Part III

Author, Year	Associations found			Potential Biases	Comments
Ford 2000 20380862 ***overlapped sample with Doyle, 2001 21064379 in Lung table**	Pubertal development was similar in VLBW and Normal BW infants. At all ages (2,5,8,14 yrs) the children who were VLBW were significantly smaller Wt/ Ht/ HC than normal BW children. Differences in Ht/ Wt/ improved over time, between VLBW and NBW, but VLBW remained smaller than Normal BW.			(None)	No data on funding source
Morley 2000 20167446	Trial 1 There was no association 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) (Growth at 9 mo) (Growth at 18 months) (Growth at 7.5-8 yrs) Trial 2 There was no association between neonatal diet (term vs preterm formula) and the Weight, Height, HC and skinfold thicknesses 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) (Growth at 18 mo) (Growth at 7.5-8 yrs)	Group A: Fed Banked donor milk (with or without supplementation with mother's milk) N=195 N=221 N=206 N= 168 N=181	Group B: Fed preterm formula:(with or without supplementation with mothers' milk) N=174 N=217 N=214 N=166 N=178		

Evidence Table 10. Studies Evaluating Association of LBW and Bone and Growth Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Avila-Diaz 2001 21334039	Study of bone mineral density using DEXA scan. Outcomes at 5 to 6 months; well preterms vs. fullterm. Full term infants (n = 16) had significantly higher (P < 0.05) bone mineral content and bone area in comparison to preterm infants (n = 26). Preterm infants had a significantly higher rate of increase in bone mineral content per day than full term infants suggesting incomplete “catch-up”.	Only "healthy" premature infants enrolled Short duration of follow-up - six months Not clear that all preterms were VLBW	Study was government funded A study of bone mineralization in preterm vs. full-terms. Not clear if all preterms were less than 1500 g.

Evidence Table 11. Randomized Controlled Trials in LBW Neonates for Growth Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Wauben 1998 98387708	Location: Canada Years of Birth: ND Mean GA (range), wk: Sample 1: 29.9±1.9 Sample 2: 30.1±1.5 Sample 3: 29.7±1.7 Mean BW (range), g: Sample 1: 1400±200 Sample 2: 1300±200 Controls: 1200±200 Male: ND Race: ND Enrolled: 37 Evaluated: 37 Number of sites: 1	BWT<1800 AGA >1 week old Full feed 5x5d Established weight gain No GI disease No long malformation	ND	Sample 1: Milk + Fortifier (12) Sample 2: Milk + Calcium phosphorus (13) Sample 3: Preterm formula-fed (12)	Randomized controlled trial (3 and 6 months)

Evidence Table 11. Randomized Controlled Trials in LBW Neonates for Growth Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Morley 2000 20167446	Location: UK Years of Birth: ND Mean GA (range), wk: Trial 1: Group A: 31.1 Group B: 31 Trial 2: Group A: 31 Group B: 31.2 Mean BW (range), g: Trial 1: Group A: 1397±297 Group B: 1387±278 Trial 2: Group A: 1399±301 Group B: 1416±306 Male: Trial 1: Group A: 53% Group B: 52% Trial 2: Group A: 47% Group B: 46% Race: ND Enrolled: 833 Evaluated: 781 Number of sites: 5	Premature BW< 1850 g Survivors of participants in the two RCTs with 2 parallel arms each (assessing effect of different neonatal diets of growth) Age 7.5-8 yrs	Lost to follow-up	Trial 1: Group A: Premature infants, breast-fed until weight 2000 g or discharge (207) Group B: Premature infants, preterm formula-fed (213) Trial 2: Group A: Premature infants, standard term formula-fed until weight 2000 g or discharge (181) Group B: Premature infants, premature formula-fed (213)	RCT: Trial 1 and 2, with 2 parallel arms in each trial (at 9 months, 18 months, 7.5-8 years)

Evidence Table 11. Randomized Controlled Trials in LBW Neonates for Growth Outcomes
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Wauben 1998 98387708	Other: Feedings: Breast, Milk+ multinutrient fortifier or breast milk + Ca + P supplement only, or preterm formula	ND	Growth: 1) Weight, length, head circumference 2) Body mass + body composition	ND
Morley 2000 20167446	Trial 1: Type of diet in early neonatal period: Banked donor breast milk vs Preterm formula (with or without supplementation with its mother's milk) Trial 2: Preterm formula vs term formula (with or without supplementation with mother's milk)	Not further specified	Trial 1: Growth: Assessment at 9 and 18 months post-term: Weight (kg), Length (cm), HC, Subscapular skinfold thickness, Body mass index Assessment at 7.5 –8 yrs: All of the above, Also weight to hip ratio Trial 2: Growth at 18 mo Growth at 7.5-8 yrs	Not further specified

Evidence Table 11. Randomized Controlled Trials in LBW Neonates for Growth Outcomes
Part III

Author, Year	Associations found				Potential Biases	Comments
Wauben, 1998		*MM+MNF*	*MM+CaCP*	*PTF*	Used a "New multinutrient fortifier" design to their specifications. Generalizability?	Study was privately funded
	Term:					
	Weight (kg):	3.3±0.3	3.2±0.4	3.5±0.4	No relation examined between feeding + neurodevelopment. Unclear that their findings have or had any potential for clinical significance.	
	Length (cm):	49.6±1.3	48.4±1.8	49.4±2.3		
	12 months:					
	Weight (kg):	9.0±0.9	9.0±0.9	9.6±1.4		
	Length (cm):	74.9±3.7	75.9±2.5	76.0±2.8	Small study- unlikely to find anything other than major differences	
	Head circumference (cm)	46.9±3.9	46.8±?	6.8±2.0		
	Whole body BMC (g)	209.9±27.1	223.0±29.2	243.9±40.6	Post-discharge crossover between breast fed→ formula fed, further dilutes effect or small #'s	
	Lean mass (%):	74.0±5.0	73±4.7	73.8±5.6		
	Fat mass (%):	23.6±5.0	24.3±4.7	23.9±5.6	No correction for multiple comparison, although it is desperately needed	
Morley, 2000	Trial 1: There was no association 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) Trial 2: There was no association 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)				(None)	? Funding

Evidence Table 12. Studies evaluating association of LBW and Nutritional Outcomes

Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Kennedy 1999 20076945 **Also in growth paper**	Location: US Years of Birth: Jan-Dec 1994 Mean GA (range), wk: 31±2.6 (26-34) Mean BW (range), g: 1534±371 (810-2000) Male: ND Race: White 93% Enrolled: 28 Evaluated: 28 Number of sites: 1	Single or twin birth BW less 2000g, follow-up at hospital clinic, completion of 3 screening visits.	ND	Preterm LBW infants (28)	Retrospective cohort (4, 9, 18 months)

Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Kennedy 1999 20076945	General : BW Other: 1) Nutrition/Growth 2) Discharge weight	ND	**Growth:** 1) weight and length 2) Head circumference	1)Denver II Developmental Test 2) "2"-Scroes

Part III

Author, Year	Associations found	Potential Biases	Comments
Kennedy 1999 20076945	**NICU discharge weight:** mean "z" score was-2.97+/- 0.53 below mean BW of term infants **18 months: mean growth in wt, hc&l :**WNL **Denver II:** normal at 18 months	Only 2 infants weighed less than 1kg Lowest GA 26 weeks 26/28 were white	No data on funding source

Evidence Table 13. Studies Evaluating Association of LBW and Other Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Saarela 1999 99345620	Location: Finland Years of Birth: 1990-1994 Mean GA: Sample 1: 21.2±2.1 Sample 2: 29.3±2.4 Mean BW: Sample 1: 993±242 Sample 2: 1174±238 Male: Sample 1: 62% Sample 2: 54% Race: ND Enrolled: 174 Evaluated: 129 Number of sites: 1	BW<1500 GA<34	Death Multiple congenital anomalies Severe toxoplasmosis Lack of repeat renal n/s	Sample 1: Preterm infants with nephrocalcinosis 26) Sample 2: Preterm infants without Nephrocalcinosis (103)	Prospective cohort (6 years)
Saarela 1999 20069000	Location: Finland Years of Birth: 1990-1994 Mean GA: Sample 1: 26.7 ±2 Sample 2: 27.2 ±2 Mean BW: Sample 1: 905 ±209 Sample 2: 957 ±226 Male: Sample 1: 30% Sample 2: 50% Race: ND Enrolled : ND for total (enrolled cases: 29) Evaluated : 40 Number of sites: 1	Cases with nephrocalcinosis: VLBW treated in the NICU of Oulu University Hospital Born during 1990-1994 Control cases: Matched to the cases VLBW: nearest to the index cases in the hospital records Difference from case's BW less than 250 g Negative renal U/S during neonatal period for nephrocalcinosis Age difference during f/up renal examination less than 8 months from the index cases.	Urinary incontinence	Sample 1: Cases with Neonatal Nephrocalcinosis(20) Sample 2: Controls, matched control cases without neonatal nephrocalcinosis (20)	Prospective comparative longitudinal study [Follow up during early childhood (not specified but the mean age during f/up assessment was 4.6 yrs)

Evidence Table 13. Studies Evaluating Association of LBW and Other Outcomes
Part I

Author, Year UI#	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Slonim 2000 20214515	Location: USA Years of Birth: 1992-1994 Mean GA: Sample 1: 1704.3 ±52.7 Sample 2: ND Mean BW: Sample 1: 30.9 ±0.2 Sample 2: ND Male: Sample 1: 57% Sample 2: 58% Race: ND Enrolled: 5927 Evaluated: 5750 Number of sites: 16	Patients with prematurity (<37 wks) and either an anatomic defect (congenital heart disease, GI tract anatomic lesion, neurologic complications (e.g., spina bifida, pulmonary lesions e.g., pulmonary agenesis)) or a prematurity related complication (BPD, Hydrocephalus, IVH, Short gut syndrome, trecheostomy, birth asphyxia, cerebral palsy) Admitted in any of the 16 participating in the study PICUs During period 12/1992-12/1994	Patients admitted in PICU in continuous cardiopulmonary resuscitation. Patients not reaching stable vital signs for > 2 hrs	Sample 1 Formerly premature patients admitted in PICU (FPP) (431) Sample 2 Their complement formerly nonpremature admitted in PICU (5.319)	Cross sectional study (FPP were assessed at a mean age of 35 mo and formerly nonprematures were assessed at a mean age of 72 mo in the 2 groups respectively)

Evidence Table 13. Studies Evaluating Association of LBW and Other Outcomes
Part II

Author, Year	Predictors	Predictor Measure	Outcomes	Outcome Measures
Saarela 1999 99345620	General : 1) BW 2) GA Audiology: 1) Furosemide Cardiovascular or Pulmonary: 1) Chronic Lung disease Other: 1) Dexamethasone 2) Furosemide use	ND	Other: Nephrocalcinosis	Described natural resolution of nephrocalcinosis

Evidence Table 13. Studies Evaluating Association of LBW and Other Outcomes
Part II

Author, Year	Predictors	Predictor Measure	Outcomes	Outcome Measures
Saarela 1999 20069000	**General:** 1) Neonatal nephrocalcinosis in VLBW infants	Nephrocalcinosis defined by the presence of medullay echogenic densities in the renal tubular pyramids	**General:** Renal function during early childhood (4-5 yrs) 1) Renal tubular function 2) Distal tubular acidification capacity 3) Renal glomerular function ➢ Serum electrolytes ➢ Venous blood pH, pCO2, Base excess, bicarbonates ➢ Urine pH, ➢ Urine ?2-microglobulin ➢ Ca/Cr ➢ Ca/Na ➢ Acetazolamide acidification test ➢ Other variables: ➢ Ccr (ml/min/1.73 m2) ➢ FENa (%) ➢ FEK (%) ➢ Tubular reabsorption of Phosphate (TRP) (%) ➢ Maximum tubular reabsorption of phosphate per glomerular filtration rate (TmP/GFR: mmol/l) 4) Kidney growth 5) Systolic blood pressure	Tubular reabsorption of phospate and maximal tubular reabsorption of phosphate per glomerular filtration rate were calculated from the baseline urine and blood sample data. Creatinine clearance were calculated by the method described by Schwartz

Evidence Table 13. Studies Evaluating Association of LBW and Other Outcomes
Part II

Author, Year	Predictors	Predictor Measure	Outcomes	Outcome Measures
Slonim 2000 20214515	**General:** 1) Prematurity with anatomic abnormalities and/or complications of prematurity (prematures vs nonprematures) 2) GA (<26 wks vs 26-32 wks vs >32 wks)	Anatomic abnormalities: Congenital heart disease Anatomical lesions of the GI tract Neurologic abnormalities: such as spina bifida Pulmonary lesions: such as pulmonary agenesis Complications of prematurity: BPD Birth asphyxia Cerebral palsy	**General:** 1) Characteristics of utilization of chronic care resources, PICU resources and characteristics of their PICU admissions: 2) Age of PICU admission 3) PICU readmissions during same hospitalization 4) Chronic care resources utilization 5) At least one chronic care resource used 6) Prior living conditions 7) Discharge location 8) PICU resource use 9) Length of stay in PICU (mean days) 10) PRISM-III score (mean)	Chronic care resources utilization: Ventilator Tracheostomy Gastrostomy Parental nutrition Prior living conditions: Home Institutions Never discharged Chronic hospital Discharge location Home Routine care Intermediate care Another PICU Chronic care PICU resource use: Ventilator Vasopressors Arterial catheter Central venous catheter PRISM-II scores: at first 24 hrs of PICU admission

Evidence Table 13. Studies Evaluating Association of LBW and Other Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Saarela 1999 99345620	Occurrence of nephrocalcinosis (NC) by birth weight. BW group / n / % without NC / % with peripheral NC / % with extensive NC < 750g / 8 / 50% / 25% / 25% 751-999 / 36 / 65% / 20% / 15% 1000-1249 / 33 / 85% / 5% / 10% 1250-1499 / 52 / 90% / 7% / 3% Association of BW with NC sigificant at P< 0.001. NC was also significantly associated (p<0.001) with: Gestational age, Presence of RDS, Presence of BPD (O2 at 28 days), Presence of CLD (O2 at 36 weeks), Furosemide use, Dexamethasone use	(None)	Study was privately funded

Evidence Table 13. Studies Evaluating Association of LBW and Other Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Saarela 1999 20069000	Predictors of renal outcome at age 4-5 yr 1) Neonatal nephrocalcinosis in VLBW children seems to lead to some signs of renal tubular dysfunction in early childhood. 2) However, distal tubular acidification, as measured by the actazolamide test 3) and glomerular function appears not to be specifically disturbed by nephrocalcinosis Renal function during early childhood (mean age: 4.6 yrs) Renal tubular function: ➢ Urinary calcium /Cr and ($p<0.004$) ➢ 2-microglobulin/Cr excretion were higher in the children with nephrocalcinosis ($p<0.05$) ➢ There was no difference in the fractional excretion of Na, K, or tubular reabsorption of phospate Distal Tubular Acidification capacity: • There was no difference in the distal tubular acidification capacity, as tested by the acetazolamide test : Abnormal response: Renal glomerular function: ➢ Creatinine clearance was no different between the 2 groups There was no difference between the 2 groups in the following : ➢ Serum electrolytes ➢ Venous blood pH, pCO2, Base excess, bicarbonates ➢ Urine pH, Kidney growth: ➢ Kidney growth was impaired by more than 2 SD ➢ There was no difference in the systolic blood pressure above 97.5 percentile ➢ None of the children had hematuria		

Evidence Table 13. Studies Evaluating Association of LBW and Other Outcomes
Part III

Author, Year	Associations found	Potential Biases	Comments
Slonim 2000 20214515	Utilization of chronic care resources and PICU resources and characteristics of their PICU admissions of former prematures with a prematurity-related complication or an anatomical deformity [431] when compared to nonprematures [5319] was: • PICU survivors: 90% vs 94% (p=0.008) • Age of PICU admission (mean): 35 mo vs 72 mo (p=0.01) • Postoperative care (%): 44% vs 40% (p=0.15) • Prior PICU admissions: 11% vs 5.5% (p=0.01) Chronic care resources utilization: • Ventilator: 7% vs 1% (p=0.001) Tracheostomy: 16% vs 2% (p=0.001) • Gastrostomy: 23% vs 4% (p=0.001) • Parental nutrition: 3% vs 0.6% (p=0.001) At least one chronic care resource used: 30% vs 5.6% , p=0.001 Prior living conditions: • Home: 90% vs 97% (p=0.001) Institutions: 3% vs 1% (p=0.001) • Never discharged: 6.5% vs 2% (p=0.002) • Chronic hospital: 3% vs 1% (p=0.001) Discharge location • Home: 11% vs 6% (p=0.001) Routine care: 63% vs 77% (p=0.001) • Intermediate care: 15% vs 10% (p=0.03) • Another PICU: 1% vs 1.6% (p=0.52) • Chronic care: 1.6% vs 0.7% (p=0.02) PICU resource use: • Ventilator: 45% vs 35% (p=0.007) • Vasopressors: 15% vs 16% (p=0.12) • Arterial catheter: 28% vs 36% (p=0.006) • Central venous catheter: 17% vs 21% (p=0.03) Limits to care (%): 5.5% vs 4% (p=0.11) Length of stay in PICU (mean days): 5.98 ds vs 3.56 ds (p=0.01) PRISM-III score AT 24 HRS (mean): 4.90 vs 4.53 (p=0.80) Those born < 26 wks had a higher utilization of chronic care resources (ventilator, trachesostomy, gastrostomy) and chronic hospital care (p< 0.006) as compared to the other prematures.	There is a strong selection bias in this study as the inclusion criteria used for the selection of the FPPs were strongly correlated with the outcomes studied (the presence of an anatomic abnormality (150/431) or a complication of prematurity (281/483) in FPPs is strongly Correlated with the utilization of chronic care resources)	Funding: Not Reported

Appendix A: MEDLINE, ERIC, PsycInfo and Healthstar Search Strategies

MEDLINE – CNS search

1. exp Infant, Low Birth Weight/
2. low birth weight.tw.
3. exp Infant, Premature/
4. 1 or 2 or 3
5. exp infant, low birth weight/ or exp infant, premature/
6. (small for gestational age or SGA).tw.
7. (preterm infant$ or infant or prematur$ or newborn).tw.
8. disab$.af.
9. limitation$.af.
10. handicap$.af.
11. impair$.af.
12. follow-up studies/
13. follow-up.tw.
14. exp Case-Control Studies/
15. case-control.tw.
16. exp Longitudinal Studies/
17. longitudinal.tw.
18. exp Cohort Studies/
19. cohort.tw.
20. (random$ or rct).tw.
21. exp Randomized Controlled Trials/
22. exp random allocation/
23. exp Double-Blind Method/
24. exp Single-Blind Method/
25. randomized controlled trial.pt.
26. clinical trial.pt.
27. (clin$ adj trial$).tw.
28. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
29. exp PLACEBOS/
30. placebo$.tw.
31. exp Research Design/
32. Comparative Study/
33. exp Evaluation Studies/
34. exp Prospective Studies/
35. 5 or 6 or 7
36. 35 and (8 or 9 or 10 or 11)
37. limit 36 to (clinical trial or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or review or review literature or review, academic or review, multicase or review, tutorial)

38. 36 and (12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34)
39. 37 or 38
40. limit 39 to human
41. limit 40 to english language
42. neuro$.tw.
43. white matter damage.tw.
44. exp intracranial hemorrhages/ or exp leukomalacia, periventricular/
45. exp Retinopathy of Prematurity/
46. ROP.tw.
47. 43 or 44
48. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
49. 2 or 5 or 6 or 7
50. 48 and 49 and 47
51. 42 or 43 or 44
52. 48 and 49 and 51
53. limit 50 to (addresses or bibliography or biography or comment or dictionary or directory or editorial or festschrift or guideline or lectures or legal cases or letter or meta analysis or news or periodical index or practice guideline or review or review literature or review of reported cases or review, academic or review, multicase or review, tutorial)
54. 52 not 53
55. limit 54 to human
56. limit 55 to english language

Eric search

1. follow-up studies/
2. follow-up.tw.
3. exp Case-Control Studies/
4. case-control.tw.
5. exp Longitudinal Studies/
6. longitudinal.tw.
7. exp Cohort Studies/
8. cohort.tw.
9. (random$ or rct).tw.
10. exp Randomized Controlled Trials/
11. exp random allocation/
12. exp Double-Blind Method/
13. exp Single-Blind Method/
14. randomized controlled trial.pt.
15. clinical trial.pt.
16. (clin$ adj trial$).tw.
17. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
18. exp PLACEBOS/
19. placebo$.tw.
20. exp Research Design/

21. Comparative Study/
22. exp Evaluation Studies/
23. disab$.af.
24. exp disabilities/
25. limitation$.af.
26. handicap$.af.
27. impair$.af.
28. exp PHYSICAL DISABILITIES/ or exp SEVERE DISABILITIES/ or exp DEVELOPMENTAL DISABILITIES/ or exp LEARNING DISABILITIES/ or exp MILD DISABILITIES/ or exp MULTIPLE DISABILITIES/
29. (small for gestational age or SGA).tw.
30. exp birth weight/
31. exp premature infants/
32. (preterm infant$ or infant or prematur$ or newborn).tw.
33. 23 or 24 or 25 or 26 or 27 or 28
34. 33 and (29 or 30 or 31 or 32)
35. 34 and (1 or 2 or 4 or 6 or 8 or 9 or 16 or 17 or 19 or 20 or 21)

GI search

174. exp enterocolitis/
175. exp cholestasis/
176. exp short bowel syndrome/
177. enterocolitis$.tw.
178. NEC.tw.
179. necrot$.tw.
180. (Total parenteral nutrition or TPN).tw.
181. cirrhosis.tw.
182. (gastrostomies or GERD or Fundoplication).tw.
183. short bowel syndrome.tw.
184. cholestasis.tw.
185. short gut.tw.
186. necrotizing.tw.
187. exp cirrhosis/

Health Care

174. rehospitalization.af.
175. costs.af.
176. costs.tw.
177. physical therapy.af.
178. exp *Occupational Therapy/
179. exp *Physical Therapy/
180. orthopedic.tw.
181. occupational therapy.af.
189. Health care resource.mp. or utilization.af. [mp=title, abstract, registry number word, mesh subject heading]
190. arthopedic.af.

191. orthopedic.af.

Healthstar

1. exp infant, low birth weight/ or exp infant, premature/
2. (small for gestational age or SGA).tw.
3. (preterm infant$ or infant or prematur$ or newborn).tw.
4. disab$.af.
5. limitation$.af.
6. handicap$.af.
7. impair$.af.
8. follow-up studies/
9. follow-up.tw.
10. exp Case-Control Studies/
11. case-control.tw.
12. exp Longitudinal Studies/
13. longitudinal.tw.
14. exp Cohort Studies/
15. cohort.tw.
16. (random$ or rct).tw.
17. exp Randomized Controlled Trials/
18. exp random allocation/
19. exp Double-Blind Method/
20. exp Single-Blind Method/
21. randomized controlled trial.pt.
22. clinical trial.pt.
23. (clin$ adj trial$).tw.
24. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
25. exp PLACEBOS/
26. placebo$.tw.
27. exp Research Design/
28. Comparative Study/
29. exp Evaluation Studies/
30. exp Prospective Studies/
31. 1 or 2 or 3
32. 31 and (4 or 5 or 6 or 7)
33. limit 32 to (clinical trial or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or review or review literature or review, academic or review, multicase or review, tutorial)
34. 32 and (8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30)
35. 33 or 34
36. limit 35 to human
37. limit 36 to english language
38. limit 37 to nonmedline

Immune

174. exp *Immunologic Diseases/ or exp *Autoimmune Diseases/ or exp *Collagen Diseases/ or exp *Immunologic Deficiency Syndromes/

Perinatal

174. antenatal steroid.tw.
175. Chorioamnioni$.tw.
176. chorionic villous sampling.tw.
177. diabet$.tw.
178. pre-eclamp$.tw.
179. 174 or 175 or 176 or 177 or 178

PsycInfo

1. follow-up studies/
2. follow-up.tw.
3. exp Case-Control Studies/
4. case-control.tw.
5. exp Longitudinal Studies/
6. longitudinal.tw.
7. exp Cohort Studies/
8. cohort.tw.
9. (random$ or rct).tw.
10. exp Randomized Controlled Trials/
11. exp random allocation/
12. exp Double-Blind Method/
13. exp Single-Blind Method/
14. randomized controlled trial.pt.
15. clinical trial.pt.
16. (clin$ adj trial$).tw.
17. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
18. exp PLACEBOS/
19. placebo$.tw.
20. exp Research Design/
21. Comparative Study/
22. exp Evaluation Studies/
23. exp Prospective Studies/
24. exp Premature Birth/
25. exp birth weight/
26. (small for gestational age or SGA).tw.
27. (preterm infant$ or infant or prematur$ or newborn).tw.
28. exp DISABILITY EVALUATION/
29. exp disabled/
30. disab$.af.
31. limitation$.af.
32. exp Mentally Retarded/
33. exp Behavior Problems/

34. exp communication skills/
35. handicap$.af.
36. impair$.af.
37. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
38. 24 or 25 or 26 or 27
39. 37 and 38
40. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
41. 39 and 40
42. 38 and 40
43. limit 42 to ("0840 follow up study" or "0850 longitudinal study" or "0860 treatment outcome study" or "0900 errata/retractions" or 1300 literature review/research review or 1400 meta-analysis)
44. 41 or 43
45. limit 44 to human
46. limit 45 to english language

ROP

174. (retinopathy of prematur$ or POP).tw.
175. exp retinopathy of prematur$/ or POP/
176. (visu$ impair$ or blindness).tw.
177. Hypoxic-Ischemic encephalopathy.tw.

Acuity

174. SNAP.tw.
175. CRIB.tw.
176. 174 or 175

Audiology

174. Lasix.tw.
175. exp lasix/
176. hearing disorder$.tw.
177. aminoglycosides.tw.

Infection

174. RSV.tw.
175. exp meningitis/
176. meningitis.tw.
177. exp sepsis/
178. (sepsis or septic).tw.
179. congenit$.tw.
180. acquired.tw.

Lung dz

174. chronic lung disease$.tw.
175. Bronchopulmonary dysplasia$.tw.

176. asthma$.tw.
177. exp asthma/
178. pulmonary function$.tw.
179. tracheostomy.tw.
180. upper airway.tw.
181. reactive airway.tw.
182. exercise tolerance.tw.
183. exp upper airway/
184. exp tracheostomy/
191. exp *Lung Diseases/ or exp *Hypertension, Pulmonary/ or exp *Lung Diseases, Obstructive/ or exp *Bronchopulmonary Dysplasia/
192. upper airway.af.
193. asthma.af.
194. pulmonary function$.af.

Medication
174. dexamethasone.tw.
175. 50-02-2.rn.
176. dexamethasone.af.

Nutrition
174. exp nutrition/
175. nutrition.tw.
176. growth disorder$.tw.
177. exp growth disorder$/
184. exp Child Nutrition Disorders/
185. exp PARENTERAL NUTRITION, TOTAL/ or exp INFANT NUTRITION DISORDERS/

Appendix B: Data Abstraction Form

Low Birth Weight and Prematurity Association with Disability

Version 11b (10/14/02)

Instructions: Circle or fill-in where appropriate Only one answer except where indicated by an *

Reviewer: __ _____ Review date: ____/_____/____

First author:_____ Year:_____ UI:_____

STUDY CHARACTERISTICS

***Country: **US UK Canada Other _____ N.D**.

Number of Sites: _____ **N.D.**

METHODOLOGY

Study Design (CHOOSE ONE):

* **Randomized Controlled Trial**

Non-randomized Comparison Trial

, **Prospective (Single arm) Cohort**

Retrospective Cohort

, **Case Series (Retrospective)**

, **Case –control (Retrospective)**

STUDY POPULATION

Year of birth of population
From_____ to _____

Inclusion criteria: _____

_____ _____

_____ _____

_____

Exclusion criteria: _____

_____

_____

Applicability of study sample to population of interest:

I. Sample representative of whole population with very low birth weight or premature infants

II. Sample is a relevant sub-group of whole population

III. Narrow sample, with limited applicability to study populat

If **II** or **III**, Why not **I**:

DEMOGRAPHICS OF INITIAL POPULATION (A)

	Sample 1	Sample 2
Description of group		
N		
Mean Age at entry (range)		
Mean GA (range)		
Mean BW (range)		
Male (%):		
Race (%):		
Other:		
Other:		

Comments:_____

DEMOGRAPHICS OF DIFFERENT FOLLOW-UP OR SUBGROUP POPULATION :

Other:		

B: Time of Evaluation:_____

	Sample 1	Sample 2
Description of group		
N		
Mean Age at eval (range)		
Mean GA (range)		
Mean BW (range)		
Male (%):		
Race (%):		
Other:		
Other:		

D: Time of Evaluation:_____

	Sample 1	Sample 2
Description of group		
N		
Mean Age at eval (range)		
Mean GA (range)		
Mean BW (range)		
Male (%):		
Race (%):		
Other:		

C: Time of Evaluation:_____

	Sample 1	Sample 2
Description of group		
N		
Mean Age at eval (range)		
Mean GA (range)		
Mean BW (range)		
Male (%):		
Race (%):		
Other:		
Other:		

E: Time of Evaluation:_____

	Sample 1	Sample 2
Description of group		
N		
Mean Age at eval (range)		
Mean GA (range)		
Mean BW (range)		
Male (%):		
Race (%):		
Other:		
Other:		

PREDICTORS OF DISBILITY EXAMINED

I

**General Predictors of Disability Examined:*

A) Birth weight

B) GA

C) SGA/IUGR

D) Maternal disease

E) Antenatal steroids

F) Chronic illness

G) Cord pH

H) Apgar score

I) Illness severity

J) Intrauterine substance abuse (Opiates, Cocaine, Ethanol. Other_____)

K) Other:_____

II **CNS Predictors of Disability Examined:*

A) Intracranial/Intraventricular hemorrhage

B) White Matter Disorder

C) Periventricular leukomalacia

D) Ventriculomegaly/ Ventricular Dilation

E) Neurological feeding disorder /Swallowing

F) Seizures

G) Hypoxic-Ischemic Encephalopathy (HIE)

H) Indomethacin

I) Other:_____

*III *Ophthalmology Predictors of Disability Examined:*

A) Retinopathy of Prematurity (ROP)

B) Other:_____

*IV *Audiology Predictors of Disability Examined:*

A) Aminoglycosides

B) Furosemide

C) Hearing screen failure

D) Other:_____

V **Cardiovascular or Pulmonary Predictors of Disability Examined:*

A) Chronic Lung Diseases

B) Bronchopulmonary dysplasia

C) Other:_____

*VI *Gastrointestinal Predictors of Disability Examined:*

A) Short gut

B) Necrotizing "enterocolitis"

C) Total Patenteral Nutrition

D) Cholestasis

E) Other:_____

*VII *Other Predictors of Disability Examined:*

A) Nutrition / Growth

B) Infectious disease

C) Immune Disorders

D) Hospital / Health care resource utilization

E) Illness Acuity

F) Dexamethasone

G) Perinatal Factors

H) Osteomalacia

I) Other:_____

J) Other:_____

K) Other:_____

How predictors defined/measured:

_____

_____

_____

_____ ND

Are the definitions correct/ appropriate? Y N **If No, Why not?**_____

_____

_____

_____

OUTCOMES EXAMINED

I ****CNS Outcomes Examined:***

- **A) Motor delay**
- **B) Cerebral palsy**
- **C) Cognitive delay**
- **D) Mental retardation**
- **E) Behavioral disorders**
- **F) School problems**
- **G) Learning disabilities**
- **H) Seizure disorder**
- **I) Post Hemorrhagic Hydrocephalus (PHH)**
- **J) Other: _____**

II ****Ophthalmology Outcomes Examined:***

- **A) Visual impairment**
- **B) Blindness**
- **C) Other: _____**

III ****Audiology Outcomes Examined***

- **A) Hearing disorders**
- **B) Deafness**
- **C) Speech**
- **D) Language**
- **E) Communication disorder**
- **F) Other: _____**

IV ****Pulmonary Outcomes Examined***

- **A) _____**
- **B) _____**

V ****Growth Outcomes Examined***

- **A) _____**
- **B) _____**

VI ****GI Outcomes Examined***

- **A) _____**
- **B) _____**

VII ****Other Outcomes Examined***

- **A) _____**
- **B) _____**

Definition of Outcomes Used by Author (methods of measure):

_____

_____

_____

_____

_____

N.D.

Are the definitions correct/ appropriate?

, **Unable to evaluate** , **Yes**

, **No**

If no, why ?

_____

_____

_____

_____

_____

RESULTS:

Group	Predictor Category	Predictors/Conditions	N	Outcome Category	Outcome of Interest/ Instruments used	% (or n/N) with Outcome	Methods of Correlation

RESULTS (cont'd):

Group	Predictor Category	Predictors/Conditions	N	Outcome Category	Outcome of Interest/ Instruments used	% (or n/N) with Outcome	Methods of Correlation

Bias Limitation::

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Internal Validity (Quality of Methods)

A Prospective (Not Retrospective). Complete reporting of methods and results (incl. inclusion/exclusion criteria, "Table 1 data,") proper reference ("gold") standard, correct analyses performed (No data inconsistency and discrepancy).

B Prospective or Retrospective. Not all criteria of A. Some deficiencies, however, unlikely to cause major bias

C Prospective or Retrospective. Significant design or reporting errors, large amount of missing information or bias. No reference standard provided or use of inappropriate reference standard.

If B or C: **Deficiency:**

_____
___

General instructions for LBW data extraction:

The form has been designed to collect all the relevant information from each article. The data on the form will allow us to fully evaluate each study's population, basic methods, relevant results (relevant for the SSA project), applicability to other children with the condition of interest, and overall quality.

For each line (or section), please circle the appropriate answer to the question (in bold) or fill in the data on the lines provided. Questions proceeded by an * can have multiple answers (such as study performed in UK and France). Please circle "N.D (no data)." if the answer to the question is not provided (eg, if information on the age of the subjects is not provided).

Study Characteristics: Self-explanatory for Country and number of sites.
Length of Following up time: Enter corrected age and average duration.
Corrected age mean: age from the obstetric due date to follow-up evaluation date.

Demographics: Enter all relevant demographic information when provided (eg, mean, standard error and range).
If median is provided, cross out mean and write in median.
For weight, please fill in the relevant data as reported in the article.
For gender and race, fill in the percentages (or the fraction).

Study population: Enter inclusion and exclusion criteria (may need to check abstract, results, and discussion sections for completeness).

Enter total number of subjects with low birth weight enrolled (including those eventually excluded or who withdrew, etc.). If only the number of subjects evaluated is reported, circle N.D.
Enter final sample size (the total number of subjects with low birth weight evaluated)
Enter total number of control subjects (presumably of normal Birth weight) enrolled and evaluated.
If reported, list reasons for withdrawal, etc. (Consider this in the assessment of possible bias later on.)

Assess **Applicability** of study to population of interest:

Consider all the data that has just been entered (study characteristics, demographics, inclusion/exclusion criteria, sample size, number and reasons for withdrawal) to determine how applicable the study is to the population of interest to us. Note that this may be a different population than the population of interest to the study authors.

First circle the question that the study is most relevant for.

Then choose one of the categories:

Category I. If sample is representative of the whole population of babies with prematurity and low birth weight condition relevant to the topic question (eg, whole population of preterm babies and infants with BW 1200-2000g). This implies a reasonable sample size, a diverse group of infants with the condition, and inclusion/exclusion criteria that will capture the whole group. Consider both who the study aimed to recruit and also who they actually included.

Category II. A relevant sub-group or subgroups of very low birth weight and prematurity, (only those with a specific, though common, condition eg: BW 1200-1500g).

Category III. A very narrow group of subjects who are a limited sample of very low birth weight and prematurity (only those with a relatively rare condition, or a non-representative demographic group e.g. crack babies)).

If Category II or III chosen, please indicate reason not in Category I (i.e., why not fully generalizable)

Methodology:

Study design: Provide one answer per line:
What is study design? (For RCT, ensure that authors state "randomized"). Prospective or retrospective cohort studies, retrospective case-control and case series may have one or more arms (i.e. treatment vs placebo).

Predictors of Disability Examined

Please circle or write in the predictors of disability that were examined in the study. These can include the factors or combination of factors predict future disability in the low birth weight and prematurity babies.

Note that the study might not clearly list the predictors evaluated. You may need to check the methods, results and discussion section to figure this out.

If provided, give the definitions the authors used for the various predictors. This may be as simple as Birth weight 1200 gms, or it may be a detailed description of their definition of HIE. This can be kept succinct.

Are the definitions used appropriate?

Outcomes Examined

Similar to predictors, circle or write in the outcomes examined.
Not all examined outcomes are necessary. Include only those that are relevant to the Topic question).
Define outcomes and determine appropriateness.

Results

The tables provided should be able to accommodate most (hopefully all) studies. Even if no statistical analysis was done by the authors, the table should be completed.

Each row will represent specific condition/predictor combination.

In a study with these four groups of subjects, each group would be put on a separate row in the first column of the table.

For each condition/predictor put the number of subjects evaluated in the second column.

In each row, write in the specific outcome evaluated. Each different outcome of interest should have its own row, or group of rows, write the instruments that being used. (How to measure outcome).

In the fourth column, give the results. What percentage of subjects in each group had the outcome of interest. You can also enter the fraction (or number of subjects), if that is easier. If other results are reported (such as odds ratio (OR)) write that in. However, please clarify what the outcome being reported is, if it's not percentage.

If there were results that are of interest, that do not conform to the table, write them in below.

Biases/Limitations:

Write down biases or limitations

Quality of Methods:

Grade quality of study (methods and reporting, not results) in 3 categories, A, B, or C.
Consider methods, definitions used, statistical analyses done, biases, etc.

A: Prospective study that is clearly reported, uses explicit and appropriate eligibility criteria, uses appropriate definitions of predictors and outcomes that are properly measured or estimated, uses appropriate statistical and analytical methods, and is free of obvious bias. Retrospective studies, irrespective of other aspects of quality, cannot be in category A. Study size should not be a factor for quality.

B: Prospective or retrospective study that does not meet qualifications of category A but deficiencies are unlikely to cause major bias.

C: Major deficiencies that cannot exclude possibility of significant bias. Insufficiently reported information.

If B or C, indicate briefly what the deficiency or deficiencies are in the paper.

Please check data information:

Check abstract numbers, tables, results and discussion for discrepancy (e.g. add them all

Appendix C: Acronyms and Abbreviations

AA	Arachidonic acid
AGA	Appropriate for gestational age
ADIT	Auditory discriminating test
BPD	Bronchopulmonary dysplasia
BSCP	Bilateral spastic cerebra palsy
BWVK	Bourdon-Wiersma-Vos concentration test for infants
BW	Birth weight
CBCL	Child Behavior Check List
CLD	Chronic lung disease
CNS	Central Nervous System
CP	Cerebral Palsy
CRIB	Clinical Risk Index for Babies
CRYO ROP	Multicenter Trial of Cryotherapy for ROP
dBHL	Decibels
DHA	Docosahexaenoic acid
DDST	Development Screening test
DQ	Developmental quotient
DR-CPR	Delivery room resuscitation
EHM-T	Exclusively human milk-fed until term CA
ELBW	Extremely Low Birth Weight
GA	Gestational age
GM	Isolated germinal matrix hemorrhage
IBR	Infant behavior record
ICH	Intracranial hemorrhage
IQ	Intelligence quotient
IUGR	Intrauterine growth retardation
IVH	Intraventricular hemorrhage
LBW	Low Birth Weight
MDI	Mental Development Index
MR	Mental Retardation
NBRS	Neurobiologic Risk Score
NBW	Normal Birth Weight
NCHS	National Center for Health Statistics
ND	No data
NEC	Necrotizing enterocolitis
NICHD	National Institute of Child Health and Development
NICU	Neonatal Intensive Care Unit
NS	Not significant
PDA	Patent ductus arteriosus
PDI	Psychomotor Developmental Indexes
PEV	Periventricular echodensities
PL	Parenchymal lesions
PMA	Postmenstrual age

PPVT	Peabody Picture Vocabulary Test
PROM	Premature rupture of membranes
PVL	Periventricular leukomalacia
RCP	Revised Class Play
RDS	Respiratory distress syndrome
ROP	Retinopathy of Prematurity
SGA	Small for gestational age
SNHL	Sensorineural hearing loss
TRF	Teacher Report Form
US	Ultrasound
VE	Ventricular enlargement
VLBW	Very Low Birth Weight
VMI	Visual-motor integration test
VM	Ventriculomegaly
WISC-R	Wechsler Intelligence Scale for Children-Revised
WMD	White Matter Damage
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

Appendix D. Acknowledgments

The Evidence-based Practice Center staff acknowledges the collaboration of the clinical experts who served on the EPC Technical Expert Panel. The EPC also acknowledges the contributions by those who acted as peer reviewers for the evidence report.

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