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)

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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]

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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) <u>At 36 months</u>: Experiment: Indomethacin group (173) Controls: Placebo (170) <u>At 54 months</u>: 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% BPD No 203 4% < 0.001 Surfactant Yes 245 13% Surfactant No 136 4% 0.003 Grade 3 or 4 IVH Yes 15 53% Grade 3 or 4 IVH No 366 8% < 0.001 PVL Yes 25 53% PVL No 352 6% < 0.001 Ventriculomegaly Yes 17 59% Ventriculomegaly 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

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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	*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	(None)	Study was government funded