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Strabismus at Age 2 Years in Children Born Before 28 Weeks' Gestation: Antecedents and Correlates

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Abstract

Children born very preterm are at greater risk of ophthalmic morbidities, including strabismus, than children born at term. We evaluated perinatal factors associated with strabismus at age 2 years in a large population of infants delivered before 28 weeks' gestation. A total of 996 infants in the multicenter ELGAN (Extremely Low Gestational Age Newborn) study who had a retinal exam in infancy and a developmental assessment at 2 years corrected age are included. Their mothers were interviewed about the pregnancy, and both mother and newborn charts were reviewed. Certified examiners administered the Bayley Scales of Infant Development-II and performed an examination of ocular alignment. Time-oriented logistic regression risk models were created to evaluate the associations of characteristics and exposures with the development of strabismus. Overall, 14% (n = 141) of the children had strabismus at 2 years, and 80% of strabismic children had esotropia. Characteristics associated with strabismus were birth before 26 weeks' gestation, severe fetal growth restriction, and maternal history of aspirin ingestion. Associated postnatal factors included a SNAP-II (Score for Neonatal Acute Physiology) illness severity value ≥30, brain ventriculomegaly, type I retinopathy of prematurity, and ventilator-dependent severe bronchopulmonary dysplasia. Strabismus in very preterm populations is associated with a number of antenatal and postnatal antecedents as well as clinical and imaging

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Author Contributions

The senior author (AL) substantially contributed to the overall conception or design of this study, and all authors (DKV, ENA, DKW, AL) contributed to acquisition, analysis, or interpretation of the data. The corresponding author (DKV) drafted the manuscript and all authors (DKV, ENA, DKW, AL) critically revised the manuscript for important intellectual content and gave final approval of the manuscript. The authors agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

correlates indicative of brain damage in these children. Routine ophthalmologic assessments in the early years can allow appropriate and timely interventions.

Keywords

ventriculomegaly; brain; retinopathy of prematurity; development; preterm birth

Strabismus often develops without apparent cause, providing a formidable challenge to deciphering disease pathogenesis and assigning causality.[1] Yet often a cause is often not apparent. Nevertheless, our knowledge of the antecedents of strabismus continues to grow. Strabismus may be present in 2% to 5% of children in the early years of life[2,3] and is a common finding in children with a history of premature birth; the lower the gestational age at birth and/or the birth weight, the higher the risk of strabismus.[4–8] Sometimes strabismus is familial[9–11] whereas at other times it is a component of a chromosomal disorder,[12–14] or accompanies malformations, especially craniofacial abnormalities.[15,16] Other risk factors and associated diagnoses include a history of retinopathy of prematurity,[17–20] severe acute-phase retinopathy of prematurity,[21–26] increased length of hospital stay (considered a proxy for severity of illness),[27] intraventricular hemorrhage with and without associated cerebral white matter damage,[22,24,25,28–31] impaired locomotor skills and hand-eye coordination,[21] cerebral palsy,[17,23,26,27] and congenital heart disease.[32] Strabismus may be associated with education problems,[33,34] social phobia and other emotional disorders,[33,35,36] and lower quality of life.[37,38]

The ELGAN (*E*xtremely *L*ow *G*estational *A*ge *N*ewborn) Study sample includes more than 1000 infants born before the 28th week of gestation who had standardized measures of neonatal exposures as well as retinal assessments in the newborn period and neurologic and developmental assessments at age 2 years.[39] As such, this sample provides an opportunity to evaluate multiple antecedents and correlates of strabismus in a high-risk sample. We used time-oriented risk models to identify significant associations between strabismus and 4 categories of variables: maternal characteristics and antenatal exposures, newborn variables, early postnatal exposures, and late postnatal exposures.

Methods

Participants

Women who delivered before 28 weeks' gestation at 1 of 14 participating centers during the years 2002–2004 were asked to participate in the ELGAN study. The enrollment and consent processes were approved by the individual institutional review boards. Mothers were approached for consent upon antenatal admission or shortly after delivery, depending on clinical circumstance and institutional preference. The study sample for this report consists of the 996 infants who had a retinal exam as clinically indicated and had a developmental assessment at 2 years' corrected age.

Demographic and Pregnancy Variables

A trained research nurse interviewed each mother in her native language after her child's birth and reviewed the maternal chart using structured data collection forms.[40] Maternal data collected included age, race, ethnicity, years of education, marriage status, gravida status, interpregnancy interval, smoking or passive exposure to smoking during pregnancy, conception assistance, prepregnancy body mass index (BMI), number of prenatal visits, and insurance status. Additionally, history of maternal fever, vaginitis, or urinary tract infection during this pregnancy was recorded, as well as exposure to medications, including aspirin, nonsteroidal anti-inflammatory medications, acetaminophen, and antibiotics.

Placenta Evaluations

Delivered placentas in a sterile exam basin were transported to a sampling room, where they were biopsied under sterile conditions; 82% of the samples were obtained within 1 hour of delivery. The microbiologic procedures and histologic procedures are described in detail elsewhere.[41–44]

Newborn Variables

The gestational age estimates were based on a hierarchy of the quality of available information. Most desirable were estimates based on the dates of embryo retrieval or intrauterine insemination or fetal ultrasound before the 14th week (62%). When those were not available, reliance was placed sequentially on a fetal ultrasound at 14 or more weeks (29%), last menstrual period (7%), and gestational age recorded in the log of the neonatal intensive care unit (1%).

The birth weight *Z* score is the number of standard deviations the infant's birth weight is above or below the median weight of infants of the same gestational age in referent samples not delivered for preeclampsia or fetal indications.[45,46] Children whose birth weight *Z* score was <–2 (ie, more than 2 standard deviations below the mean in the standard data set) are identified as severely growth restricted, whereas those whose birth weight *Z* score was ≥–2 yet <–1 (ie, between 1 and 2 standard deviations below the mean) are identified as moderately growth restricted.

We collected all the physiology, laboratory, and therapy data for the first 1 hours needed to calculate a SNAP (Score for Neonatal Acute Physiology)-II score.[47] SNAP-II includes points for lowest mean blood pressure, lowest temperature, lowest pH, respiratory dysfunction (the lowest of PaO_2/FiO_2 rations at 3 points), low urine output, and seizures. We arbitrarily selected a SNAP-II value of 30 or more as high, which identified 28% of our sample.

Infants were classified by their extreme blood gas measurements (lowest and highest PaO_2, PCO_2, and pH) on postnatal days 1, 2, and 3.[48] We classified infants by whether or not their extreme value each day was in the extreme quartile for their gestational age (23–24, 25–26, and 27 weeks), and we required that an infant be in the extreme quartile on at least 2 of the 3 days to be considered "exposed" to such extremes.

Bacterial cultures were reported for each of the first 4 postnatal weeks; we define early bacteremia as evident in the first week and late bacteremia as evident in weeks 2, 3, or 4. The recovery of an organism from blood was reported, but details about the organism were not. An infection was identified as definite when a pathogen was reported.

For each of the first 28 postnatal days, information was collected about receipt of hydrocortisone, dexamethasone, and antibiotics. Information about receipt of a blood product was recorded on postnatal days 7, 14, 21, and 28. More than half the newborns received a blood product transfusion on at least 3 of these 4 days.

Ophthalmologic Examinations

Participating ophthalmologists used standardized data collection forms for retinopathy of prematurity examinations, with definitions of terms according to the International Committee for Classification of Retinopathy of Prematurity.[49] Examinations were performed according to guidelines,[50] with the first examination occurring between the 31st to 33rd postmenstrual week and continuing as clinically indicated until normal vascularization began in zone III, infants reached 45 weeks postmenstrual age without severe retinopathy of prematurity, or full vascularization occurred.

Acute phase retinopathy of prematurity was categorized based on severity of disease, including presence of retinopathy of prematurity in zone I, stage 3 or higher retinopathy of prematurity, presence of plus disease, or treatment warranted prethreshold (type I) retinopathy of prematurity. Type 1 retinopathy of prematurity is defined as any retinopathy of prematurity in zone I with plus disease or stage 3 without plus disease, and in zone II, stage 2 or stage 3 with plus disease.[51]

Protocol Head Ultrasound Scans and Interpretation

Routine scans using digitized high-frequency transducers (7.5 and 10 MHz) were performed and included the 6 standard quasicoronal views and 5 sagittal views using the anterior fontanel as the sonographic window.[52] Standard data collection forms were used, and all scans were read by 2 independent readers masked to clinical information.[53] When the 2 readers differed in their recognition of moderate/severe ventriculomegaly or an echolucent/hypoechoic lesion, the films were sent to a third (tie-breaking) reader.

Diagnoses

ELGANs were classified into 3 mutually exclusive groups: those with consistently low FiO_2 (an FiO_2 <0.23 on all days between days 3 and 7 of life and receiving FiO_2 ≤0.25 on day 14), those with pulmonary deterioration (PD; an FiO_2 <0.23 on any day between 3 and 7 days and receiving FiO_2 >0.25 on day 14), and those with early and persistent pulmonary dysfunction (an FiO_2 ≥0.23 on all days between days 3 and 7 of life and receiving FiO_2 >0.25 on day 14).[46]

After discharge, details were collected about the apparent need for respiratory care at 36 weeks postmenstrual age (PMA) along with discharge diagnoses. The diagnosis of bronchopulmonary dysplasia was based on whether or not the child was receiving

supplemental oxygenation at 36 weeks postmenstrual age. The diagnosis of ventilator-dependent severe bronchopulmonary dysplasia was applied if the child was dependent on both supplemental oxygen and mechanical ventilation.[1]

The child's necrotizing enterocolitis status was classified according to the modified Bell staging system.[54]

Developmental Assessment at 24 Months

Developmental assessments were performed as close to the age of 24 months corrected age as possible. Procedures to standardize the neurologic examination and minimize examiner variability were previously described in detail.[55] The topographic diagnosis of CP (quadriparesis, diparesis, or hemiparesis) was based on an algorithm using these data.[56]

Visual interaction for each child was assessed under the child's optimal state of wakefulness and cooperation. The ability to fix and follow on faces and toys was recorded as present or absent. Assessment for strabismus was performed using cover/uncover testing, and the examiner identified the presence of esotropia, exotropia, hypotropia, or hypertropia. Visual field assessment was performed by confrontational testing to 4 quadrants using an engaging object, such as a finger puppet.

Certified examiners administered and scored the Bayley Scales of Infant Development–Second Edition.[57] Mental Development Index scores <55 and Psychomotor Development Index scores <55 were chosen as outcomes because they are 3 standard deviations below the expected mean and therefore constitute severe impairment.[58] The examiners were asked to rate the child on the Gross Motor Function Classification System, separate from the neurologic examination. A level of ≥2 indicates that the child cannot walk.

The head circumference was measured at the time of the developmental assessment as the largest possible occipital-frontal circumference, rounded to the closest 0.1 centimeter. All head circumferences are presented as *Z* scores because children were assessed at different gestational ages at birth (23–27 weeks) and at different approximations of 24 months corrected age (range: 16–44 months corrected age, with 68% assessed at 23–25 weeks corrected age). *Z* scores of head circumference and body weight at 2 years were based on standards in the Centers for Disease Control and Prevention (CDC) data sets.[12]

Data Analysis

Because there were no differences between rates of esotropia and exotropia in relationship to the presence of ocular or brain disorders at 2 years corrected age, we combined them into the 1 entity in all analyses (Table 1). We created Tables 2 to 5 to evaluate the occurrence of maternal, pregnancy, neonatal, and postnatal characteristics among children with and without strabismus. Finally, because postnatal phenomena can be influenced by antepartum phenomena, we fit logistic regression models in which risk factors were ordered in a temporal pattern, so that the earliest-occurring predictors/covariates of an outcome were entered first and were NOT displaced by later-occurring covariates (Table 6).[59] For these time-oriented logistic regression risk models (TORMs), we categorize sets of antecedents/covariates by the time they occur or are identified (eg, antenatal/neonatal, early postnatal,

and later postnatal). We used a step-down procedure seeking a parsimonious solution without interaction terms. These models allowed us to calculate odds ratios and 95% confidence intervals. The maternal factors and infant characteristics at birth were considered first ("antenatal/neonatal"), followed by events and measures that occurred in the first 4 weeks of life ("early post-natal"), followed by events and diagnoses that occurred after 4 weeks until a corrected gestational age of approximately 40 weeks, or discharge from the neonatal intensive care unit ("late post-natal").

Results

Sample Description (Table 1)

Consent for participation was obtained from 1249 mothers of 1506 eligible infants. Overall, 1248 of the infants had a retinal exam as clinically indicated for retinopathy of prematurity screening between 31 and 33 weeks postmenstrual age, and 1179 of them survived to 2 years' corrected age. At the 2-year developmental assessment, 996 children were evaluated for strabismus. The 183 children who were not evaluated for strabismus were slightly more likely to be born to a single mother without a college education and to have been of younger gestational age at birth.

At the 2-year assessment, 141/996 (14%) of infants had strabismus. Of these strabismic children, 79% showed an esodeviation, 18% were exotropic, and 2% had a deviation that varied from esotropia to exotropia.

Strabismic children, whether esotropic or exotropic, were more likely than their non-strabismic peers to have impaired fixation, a visual field deficit, a history of type I retinopathy of prematurity, cerebral palsy, inability to walk, a very low Mental Development Index, a very low Physical Development Index, and very small head circumference and body weight Z-scores.

Maternal Characteristics and Exposures (Table 2)

Children who developed strabismus were less likely than their peers without strabismus to have a mother who graduated from college (26% vs 35%). In addition, their mothers were more likely to have been obese (prepregnancy BMI ≥30) before the onset of the pregnancy (27% vs 20%). No other maternal sociodemographic characteristic discriminated between children with and without strabismus.

Antenatal and Delivery Illnesses, Exposures, and Characteristics (Table 3)

Mothers of children with strabismus were more likely than others to have consumed aspirin during the pregnancy (9% vs 5%) and less likely than others to have received a complete course of antenatal steroid course (59% vs 65%). The children who developed strabismus were more likely than their nonstrabismic peers to have been born at the lowest gestational age (23–24 weeks: 29% vs 18%), lowest birth weight (≤750 g: 51% vs 34%), and the lowest birth weight *Z* score (≤–2: 9% vs 5%).

Placenta Characteristics (Data Not Shown)

No placenta histologic characteristic discriminated between those with and without strabismus. Similarly, children who had strabismus did not differ from their peers in the tendency of their placenta to harbor any organism, or any specific organism or group of organisms.

Early Postnatal Characteristics and Exposures (Table 4)

Children with strabismus were more likely than others to have a high SNAP-II (≥ 30: 36% vs 20%). They were also more likely to have had a PCO_2 in the top quartile on 2 of the first 3 days (31% vs 20%), a pH in the lowest quartile on 2 of the first 3 days (27% vs 19%), "late" bacteremia (ie, during the last 3 weeks of the first postnatal month; 35% vs 23%), and to receive mechanical ventilation assistance on postnatal day 14 (71% vs 56%) and at post-menstrual week 36 (19% vs 7%).

Compared to children who did not develop strabismus, those who did were more likely to have received a postnatal corticosteroid (hydrocortisone: 35% vs 23%; dexamethasone: 13% vs 7%), a blood or blood product transfusion during 3 of the first 4 postnatal weeks (72% vs 54%), as well as an antibiotic during weeks 2–4 (86 vs 77%).

Diagnoses (Table 5)

Children who developed strabismus were more likely than others to have ventriculomegaly (18% vs 8%) or an echolucent lesion (11% vs 6%) on a cranial ultrasound scan, and to have been given a diagnosis of pulmonary interstitial emphysema (27% vs 13%), advanced necrotizing enterocolitis (7% vs 3%), type I retinopathy of prematurity (28% vs 9%), and ventilator-dependent severe bronchopulmonary dysplasia (20% vs 7%). Type I retinopathy of prematurity developed in 12% of this cohort, and of these children, 34% had strabismus at the 24-month assessment.

Time-oriented Strabismus Risk Model (Table 6)

Despite a wide variety of risk factors offered from the antenatal/neonatal epoch, the time-oriented risk model retained only 3, aspirin ingestion (odds ratio = 2.1, 95% confidence interval = 1.1, 4.1), low gestational age (23–24 weeks odds ratio = 2.8, 95% confidence interval = 1.7, 4.8; 25–26 weeks odds ratio = 1.8, 95% confidence interval = 1.1, 2.9), and severe growth restriction (odds ratio = 2.3, 95% confidence interval = 1.2, 4.6). Of the 7 early postnatal variables considered, 3 provided statistically significant supplemental information, SNAP II ≥30 (odds ratio = 1.8; 95% confidence interval = 1.2, 2.7), postnatal steroid treatment (odds ratio 1.7, 95% confidence interval = 1.1, 2.6), and bacteremia during weeks 2 to 4 (odds ratio = 1.6, 95% confidence interval = 1.1, 2.3). Of the 6 late postnatal variables offered the time-oriented model, 3 added unique discriminating information, ventriculomegaly (odds ratio = 2.3; 95% confidence interval = 1.3, 3.9), type I retinopathy of prematurity (odds ratio = 2.5; 95% confidence interval = 1.5, 4.0), and ventilator-dependent severe bronchopulmonary dysplasia (odds ratio = 2.8; 95% confidence interval = 1.6, 4.8).

Discussion

Our main findings are that strabismus at 2 years of age is associated with maternal consumption of aspirin during pregnancy; lower gestational age at birth; severe intrauterine growth restriction; a high illness-severity score during the first 12 postnatal hours; receipt of a corticosteroid postnatally; documented bacteremia during the second, third, or fourth postnatal weeks; ventriculomegaly on a head ultrasonographic scan; type I retinopathy of prematurity; and ventilator-dependent severe bronchopulmonary dysplasia. Use of a time-oriented risk model helps identify, in stepwise fashion, significant early events that may contribute to later diagnoses. The observation that several diagnoses co-occur with strabismus (such as cerebral palsy, poor motor or cognitive function, or impaired fixation behavior) raises the question of whether strabismus is a consequence of the disorders or their antecedents. Unfortunately, we are not able to answer this question without additional analyses. Our findings also suggest that closer ophthalmologic follow-up may be needed for those infants identified to have had an exposure or characteristic that is an early antecedent.

Of all the possible antenatal risk factors studied, only maternal ingestion of aspirin was found to provide significant information. Only a relatively small number of infants, however, had a mother who took aspirin during pregnancy (51/996, 5% of the cohort), and only 9% of the children with strabismus had exposure to maternal aspirin compared to 5% of children without strabismus. Is it the aspirin, or the indication for the aspirin, that increases strabismus risk? Aspirin consumption is likely to represent indicators of inflammatory phenomena (eg, malaise, fever), and presumed risk of pregnancy-induced hypertension.[60] If risk of pregnancy-induced hypertension was the indication, we would have likely seen an increased prevalence of strabismus among children delivered for preeclampsia. In support of an inflammatory indication is the observation that women in our sample who consumed aspirin were more likely than other women to have had a placenta that was inflamed and harbored an anaerobe.[61] The children of women who consumed aspirin were also at an increased risk of quadriparetic cerebral palsy.[61]

Low-dose aspirin consumed by women at risk for pregnancy-induced hypertension, preeclampsia, or severe fetal growth restriction has not been associated with neurobehavioral abnormalities in the offspring.[62,63] Whether prescribed or taken by the gravida for symptomatic relief, aspirin ingestion by mothers in the ELGAN Study is more likely to be an indicator of potentially brain-damaging exposures rather than a cause of brain damage and its correlates, including strabismus.

Others have reported that strabismus is more common among children with a history of birth at very early gestational ages and low birth weight.[4–8,64] All too often, studies of the relationship between gestational age and strabismus risk have been marred by viewing birth weight as a substitute for, or a competitor to, gestational age, by not including indicators of intrauterine growth restriction. Among higher quality studies, by and large, the lower the gestational age, the higher the risk of strabismus. Unfortunately, the studies very enormously in size and the groups compared. We, too, found that low gestational age and severe intra-uterine growth restriction are antecedents of strabismus. In the ELGAN study population,

these are also antecedents of bronchopulmonary dysplasia,[65] type I retinopathy of prematurity,[66] and early neurocognitive impairment.[67]

Early postnatal characteristics associated with strabismus were a high SNAP-II, ventriculomegaly, and type I retinopathy of prematurity. The SNAP-II[47] is a validated tool to assess newborn illness severity based on derangements in 6 physiologic measures (blood pressure, temperature, P_aO_2/FiO_2 ratio, lowest serum pH, multiple seizures, urine output) taken within 12 hours of neonatal intensive care unit admission. Early physiologic derangements in isolated parameters in our population did not pose additional strabismus risk, but the SNAP-II provides an overall assessment of early physiologic instability in an infant. In the ELGAN study sample, a high SNAP was associated with increased risk of ventriculomegaly and very low mental and motor development indices.[68] Most previous studies evaluating the association of strabismus with abnormal head ultrasonographic findings have concentrated on intraventricular hemorrhage rather than presence of ventriculomegaly alone, which can, but need not, occur as a consequence of severe intraventricular hemorrhage.[22–25,28–31]

The same set of circumstances that lead to damage in the brain (with resultant neurodevelopmental abnormalities) can also lead to problems in the eye (retinopathy of prematurity).[30] Severe acute phase retinopathy of prematurity, usually described as stage 3 or greater, has been linked with later development of strabismus[21–26] and we confirm an association for infants with a history of treatment warranted prethreshold retinopathy of prematurity. The 34% rate of type I retinopathy of prematurity in our cohort (defined by gestational age <28 weeks at birth) was the same as the rate of high-risk prethreshold retinopathy of prematurity reported in the Early Treatment for Retinopathy of Prematurity cohort (defined by birth weight <1251 g) who developed high-risk prethreshold retinopathy of prematurity.[69,70] Although we found a correlation with a child's inability to fix and follow, evaluation of ocular structural outcomes, grating acuity measurements, and other measures such as refraction or presence of amblyopia were not part of our data collection process.

In the late postnatal period, infants with strabismus were more likely than their non-strabismic peers to have ventilator-dependent severe bronchopulmonary dysplasia, and at age 2 years, very low Bayley mental and motor development scores, and an inability to walk. These diagnoses are contemporaneous correlates, so that no causal relationships are implied. Indeed, these findings are in keeping with our view that we cannot eliminate the possibility that the antecedents of strabismus are, in fact, the antecedents of the very disorders associated with strabismus.

Our use of time-oriented risk models allowed us to evaluate antecedents in chronologic sequence, thereby providing us with the opportunity to identify the antecedents of antecedents, and to avoid attributing to later-occurring characteristics and exposures what is more appropriately attributed to earlier phenomena. This is especially important in light of our claim that the antecedents of strabismus might more appropriately be viewed as antecedents of the brain damage that characterizes disorders associated with strabismus.

Strengths of this study include prospective, detailed data collection of multiple potential antecedents and correlates of morbidity in extremely preterm infants, the very large number of infants studied, the use of gestational age rather than birth weight to define the population, and analysis using a time-oriented risk model so that later influences could be evaluated in light of earlier influences. Limitations of this study include lack of other ophthalmologic outcomes to correlate with development of strabismus. Additionally, the 24-month assessment was typically performed by neurologists, which might lead to underdiagnosis of more subtle forms of strabismus. Because the children who were not available for the neurologic examination at 2 years tended to be of lower gestational age, strabismus and other morbidities may have been underrepresented.

We did not collect information about blood transfusion on every possible day, in large part because most newborns in the ELGAN study received small amounts of blood frequently. Indeed, more than half of all children who did not develop strabismus received a transfusion on 3 of the 4 individual day assessments, and almost three-quarters of infants who developed strabismus did so. Nevertheless, this intermittent assessment should be viewed as a limitation because it is not equivalent to a daily assessment for transfusion.

This study confirms the need for continued ophthalmologic surveillance of very preterm newborns for strabismus, particularly those born before the 28th week of gestation with a history of type I retinopathy of prematurity, or later, who have demonstrated significant motor and cognitive impairment (including cerebral palsy or an inability to walk independently). At a minimum, follow-up at 1 year adjusted age seems prudent, with intervals after that based on exam findings, with the recognition that strabismus prevalence rates among extremely preterm children continue to increase in the early childhood years.

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Appendix

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Table 1

Visual, Retinal, and Brain Disorders Associated With Strabismus.[a]

		Strabismus		
		Yes	No	Row n
Visual field deficit	Yes	18	3	49
Impaired fixation	Yes	14	4	53
Type 1 ROP[b]	Yes	28	9	118
Cerebral palsy	Quadriparesis	18	4	58
Diagnosis	Diparesis	7	3	35
	Hemiparesis	4	2	19
GMFCS	≥2	16	3	49
MDI[c]	<55	28	12	137
	55–69	17	10	107
PDI[d]	<55	32	13	146
	55–69	22	13	142
2-year head circumference *Z* score[e]	<−2	21	8	99
2-year body weight Z-score[e]	<−2	6	2	27
Maximum column n		141	855	996

Abbreviations: GMFCS, Gross Motor Function Classification System.

[a] These are column percentages except for numbers in Row n column and Column n row.

[b] Retinopathy of prematurity, treatable by ETROP criteria.

[c] Mental Development Index of the Bayley Scales for Infant Development II; scores of 55–69 are 2 standard deviations below the expected mean and scores <55 are 3 standard deviations below the expected mean.

[d] Motor Development Index of the Bayley Scales for Infant Development II; scores of 55–69 are 2 standard deviations below the expected mean and scores <55 are 3 standard deviations below the expected mean.

[e] CDC standard.

Table 2

Column Percentages of Maternal Characteristics Associated With Strabismus.

		Strabismus		
Maternal characteristics		**Yes**	**No**	**Row n**
Racial identity	White	61	60	589
	Black	28	28	273
	Other	11	12	119
Hispanic	Yes	14	11	116
Maternal age, y	<21	16	13	131
	21–35	64	67	664
	>35	21	20	201
Years of education	<12	18	15	151
	≥12, <16	56	50	489
	≥16	26	35	964
Married	Yes	55	59	579
Public insurance	Yes	39	39	383
Smoking in pregnancy	Yes	17	13	129
Passive smoking	Yes	29	24	236
Primagravida	Yes	42	41	397
Interpregnancy interval	<1 y	18	20	112
	1–2 y	35	29	168
	≥2 y	46	52	289
Conception assistance	Yes	20	22	212
Number of prenatal visits	≥10	28	31	297
Prepregnancy body mass index	<18.5	7	8	76
	18.5, <25	54	50	481
	25, <30	11	22	195
	≥30	27	20	203
Maximum column n		141	855	996

Table 3

Column Percentages of Pregnancy or Delivery Exposures and Characteristics Associated With Strabismus.

		Strabismus		
Pregnancy characteristics		**Yes**	**No**	**Row n**
Antenatal aspirin	Yes	9	5	51
Antenatal steroid course	Complete	59	65	635
	Partial	28	25	253
	None	17	10	106
Pregnancy disorder leading to preterm delivery	Preterm labor	45	45	450
	pPROM	23	22	219
	Preeclampsia	13	13	129
	Abruption	8	11	107
	Cervical insufficiency	4	5	50
	Fetal indication	6	4	41
Duration of labor, h	0	25	24	238
	>0 to ≤12	20	22	219
	>12	55	54	539
Duration of rupture of membranes, h	<1	56	59	583
	1–24	16	15	155
	>24	28	26	258
Magnesium	None	35	33	324
	Tocolysis	51	55	537
	Seizure prophylaxis	14	13	126
Cesarean delivery	Yes	65	67	668
Fever[a]	Yes	7	7	66
Sex	Male	51	51	511
Type of gestation	Multiple	33	35	342
Gestational age, wk	23–24	29	18	193
	25–26	50	46	467
	27	21	36	336
Birth weight, g	≤750	51	34	360
	750–1000	35	46	444
	>1000	14	20	192
Birth weight *Z* score[b]	<−2	9	5	55
	≥−2, <−1	17	12	130
	≥−1	74	83	811
Maximum column n		141	855	996

Abbreviation: pPROM, preterm premature rupture of membranes.

[a] Within the interval from before delivery to 48 hours postdelivery.

[b] Yudkin standard.

Table 4

Column Percentages of Early Postnatal Characteristics Associated With Strabismus.

		Strabismus		
Postnatal characteristics		**Yes**	**No**	**Row n**
Score for Neonatal Acute Physiology (SNAP-II), 0–12 h	<20	40	54	509
	20–29	24	26	250
	≥30	36	20	219
Lowest quartile P_aO_2[a]	Yes	23	20	174
Highest quartile P_aO_2[a]	Yes	20	21	172
Lowest quartile PCO_2[a]	Yes	25	21	182
Highest quartile PCO_2[a]	Yes	31	20	182
Lowest quartile pH[a]	Yes	27	19	171
Bacteremia during first postnatal week	None[b]	55	58	576
	Presumed	35	36	356
	Definite	9	6	64
Bacteremia during postnatal weeks 2–4	None[b]	47	63	600
	Presumed	18	14	144
	Definite	35	23	249
Postnatal steroid[c]	Yes	35	18	195
Transfusion[d] in ≥3 wk	Yes	72	54	562
Antibiotic, week 2–4	Yes	86	77	777
Conventional mechanical/high-frequency ventilation on day 14	Yes	71	56	577
Conventional mechanical/high-frequency ventilation at 36 wk	Yes	19	7	85
Maximum column n		141	855	996

[a] Extreme blood gas measure quartile for gestational age on 2 of the first 3 postnatal days.

[b] None or suspected.

[c] Hydrocortisone or dexamethasone.

[d] Packed cells or whole blood.

Table 5

Column Percentages of Diagnoses and Classifications Associated With Strabismus.

		Strabismus		
Diagnoses and classifications		**Yes**	**No**	**Row n**
Ventriculomegaly[a]	Yes	18	8	94
Echolucent lesion[a]	Yes	11	6	68
Quartile of growth velocity[b]	Low	27	24	240
	Low middle	19	26	244
	Middle high	27	26	255
	High	27	24	241
Patent ductus arteriosus	Yes	69	67	674
Pneumothorax	Yes	10	7	70
PIE[c]	Yes	27	13	152
Pulmonary hemorrhage	Yes	4	3	29
Respiratory group classification	EPPD	51	40	405
	PD	33	39	367
	Low FiO_2	16	21	192
Necrotizing enterocolitis (Bell stage)	IIIb: advanced	7	3	32
	Isolated perforation	4	3	31
	None[c]	89	95	933
ROP: stage	3–5	50	23	269
ROP: plus disease	Yes	23	8	97
ROP: Type I[d]	Yes	28	9	118
Bronchopulmonary dysplasia	Ventilator-dependent[e]	20	7	85
	Not ventilator-dependent[f]	46	42	424
	No	34	51	485
Maximum column n		141	855	996

Abbreviations: EPPD, early and persistent pulmonary dysfunction; PD, pulmonary deterioration; PIE, Pulmonary interstitial emphysema; ROP, retinopathy of prematurity.

[a] On cranial ultrasound scans in the neonatal intensive care unit; alone or with other lesions.

[b] 1000*((wt28−wt7)/wt7)/21; units: g/kg/d.

[c] Includes less severe disease.

[d] Satisfied ET-ROP criteria for ablative surgery

[e] On ventilator as well as oxygen at 36 weeks postmenstrual age.

[f] On oxygen, but not on ventilator, at 36 weeks postmenstrual age.

Table 6

Risk ratios (95% Confidence Intervals) of Strabismus at Age 2 Years Associated with Antecedents and Correlates.[a]

		Odds ratios (95% confidence intervals)		
Occurred/identified	**Antecedent/correlate**	**Ante-/neonatal**	**Early postnatal**	**Late postnatal**
Antenatal/neonatal	Mother consumed aspirin	**2.1 (1.1, 4.1)**	**2.1 (1.1, 4.2)**	**2.1 (1.02, 4.2)**
	Gestational age 23–24 wk	**2.8 (1.7, 4.8)**	**1.9 (1.1, 3.6)**	1.4 (0.8, 2.6)
	Gestational age 25–26 wk	**1.8 (1.1, 2.9)**	1.5 (0.9, 2.4)	1.3 (0.8, 2.1)
	Birth weight *Z* score <–2	**2.2 (1.1, 4.2)**	**2.0 (1.00, 2.7)**	1.6 (0.8, 3.2)
Early postnatal	SNAP-II ≥30		**1.8 (1.2, 2.7)**	**1.6 (1.00, 2.4)**
	Postnatal steroid[b]		**1.7 (1.1, 2.6)**	1.4 (0.9, 2.2)
	Definite late bacteremia[c]		**1.6 (1.1, 2.3)**	1.4 (0.9, 2.1)
Late postnatal	Ventriculomegaly			**2.3 (1.3, 3.9)**
	Type I ROP			**2.5 (1.5, 4.0)**
	BPD ventilator-dependent[d]			**2.8 (1.6, 4.8)**

Abbreviations: BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; SNAP-II, Score for Neonatal Acute Physiology.

[a] These are calculated from time-oriented logistic risk models. Variables were retained in the model if the *P* value when they first entered the model was <.01. Bold items are statistically significant.

[b] Hydrocortisone or dexamethasone.

[c] Culture proven bacteremia in weeks 2–4.

[d] On ventilator as well as oxygen at 36 weeks postmenstrual age.