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Perinatal Risk Factors for Strabismus

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Abstract

Background: Little is known about the etiologic factors underlying strabismus. We undertook a large cohort study to investigate perinatal risk factors for strabismus, overall and by subtype.

Methods: Orthoptists reviewed ophthalmologic records for Danish National Birth Cohort children examined for strabismus in hospital ophthalmology departments or by ophthalmologists in private practice. Information on perinatal characteristics was obtained from national registers. We used log-linear binomial regression and polytomous logistic regression to estimate risk ratios for strabismus overall and by strabismus subtype, respectively.

Results: Among 96 842 DNBC children born in Denmark between 1996 and 2003, we identified 8783 children who had been evaluated for strabismus. Ophthalmologic records were available for 5655 of these children, of whom 1321 were diagnosed with strabismus. In multivariable analysis, low birth weight, prematurity, large head circumference and presence of congenital abnormalities were all associated with increased risk of strabismus. Presence of congenital abnormalities was more strongly associated with exotropia than with esotropia. Of 183 exotropia cases, 40 (22%) had a congenital abnormality. While not associated with esotropia, delivery by Cesarean section was associated with exotropia (RR=1.65; 95% CI 1.16-2.34). After adjustment for birth weight, Apgar score at five minutes, multiple gestation and parental ages were not associated with strabismus overall.

Conclusions: Congenital abnormalities, low birth weight, prematurity, and large head circumference were independent risk factors for strabismus. Differences in risk factors for esotropia and exotropia suggest that strabismus subtypes may have different underlying etiologies. The proportion of exotropic children with congenital abnormalities suggests that a large angle constant exotropia in an infant should alert physicians to the possibility of a congenital malformation.

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Medical Subject Headings: strabismus, risk factors, birth weight, prematurity, Cesarean section, congenital abnormalities, head circumference

For Review Only

Strabismus is a common disorder of the eyes, with a reported childhood prevalence of 2%-6% in Western countries.(1-6) Left uncorrected, strabismus can result in amblyopia, which may lead to permanent loss of vision.

Little is known about the etiologic factors underlying strabismus, which probably encompasses multiple etiologically distinct entities. Many types of strabismus are typically detected in childhood, suggesting that events occurring during the perinatal period might be important. Several investigators have reported low birth weight as a risk factor for strabismus.(3;7-14) Although some studies have found prematurity to be associated with strabismus,(3;6;11;13-15) no study has demonstrated an association between gestational age at birth and strabismus after adjusting for birth weight.(14;16;17) Studies addressing other perinatal risk factors for strabismus are limited.(3;6;13;17)

The sparse scientific literature on perinatal risk factors for strabismus prompted us to undertake a large population-based cohort study to address this issue. Specifically, we investigated the effect of maternal and paternal age, maternal pre-eclampsia, multiple gestations, birth weight, gestational age, head circumference, Cesarean delivery, neonatal asphyxia, Apgar score 5 minutes post-delivery, neonatal septicemia, and the presence of congenital abnormalities on the risk of strabismus, overall and by strabismus subtype.

Methods

Data Sources

Our study cohort consisted of the 96 842 children born alive between 1996 and 2003 to women participating in the Danish National Birth Cohort (DNBC).(18;19) We collected information from national registers concerning variables of interest and the whereabouts of ophthalmologic records, if any, for each child. We used the unique personal identification number (PIN),

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assigned to all Danish residents (Danish citizens and persons with Danish residence permits) by the Danish Civil Registration System since 1968, to link individual-level information from the national registers for each cohort child.

Medical Birth Register

The Medical Birth Register has recorded live births and stillbirths in Denmark since 1973. The register contains information on birth characteristics (e.g. birth weight, gestational age, Apgar score at 5 minutes), birth outcomes, and delivery complications, recorded by midwives attending the delivery.

National Patient Register

Reporting of data on Danish residents’ hospital admissions and outpatient visits has been mandatory since 1977 and 1994, respectively. The National Patient Register contains detailed information on date of hospitalization or outpatient visit, codes for discharge diagnoses, and codes for any surgical procedures.(20) Since 1994, the National Patient Register has coded discharge diagnoses using the 10th Revision of the International Classification of Diseases (ICD-10) and surgical procedures using Nordic Medico-Statistical Committee Classification of Surgical Procedures (NCSP) codes.

Health Security System

Health care is free of charge for all residents of Denmark. The Danish health care system reimburses specialists in private practice for their services. The Health Security System records these reimbursements and contains detailed information on procedures and examinations performed (although no information on specific diagnoses).

Case Ascertainment

We linked DNBC information with information from the National Patient Register (information available up to March 16th, 2006) and the Health Security System (information available up to December 31st, 2005) to identify DNBC children diagnosed with or suspected of having strabismus. Specifically, we searched the National Patient Register for strabismus diagnoses (ICD-10 codes H49-H51) and strabismus operations (NCSP codes KCEA-KCEW) to identify children with a hospital-confirmed strabismus diagnosis and children who had undergone strabismus surgery. We also searched the Health Security System for the strabismus evaluation code (19.2001) to identify children who had been evaluated for strabismus by an ophthalmologist in private practice (OPP).

The search of the National Patient Register yielded 447 children with strabismus-related visits to ophthalmology and/or pediatric departments. The search of the Health Security System identified 8674 children who had visited 186 different OPPs. We subsequently requested ophthalmologic records for all children identified by the two searches. The number of children for whom records were requested (n=8783) does not equal the sum of the children identified in the two searches (9121) because there was some overlap between children identified using the two methods. We obtained records for 5655 (64%) of 8783 children evaluated for strabismus by an OPP and/or diagnosed with strabismus at a hospital department. We could not obtain records for 3127 seen by 66 OPPs, due mainly to OPP refusal to participate (n=31), non-response (n=23), or retirement (n=10). Only one of the missing records was a hospital chart.

Two experienced orthoptists evaluated the ophthalmologic records and recorded specific strabismus subtype diagnosis (if any), date of diagnosis, and any concomitant disease relevant to strabismus (central nervous system, neurologic or facial bone disease). The orthoptists classified strabismus into the following groups: exotropia, congenital esotropia, accommodative esotropia, other esotropia, and other strabismus. Congenital esotropia was defined as an esotropia with

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onset before the age of 6 months that could not be corrected with glasses. Accommodative esotropia was defined as an esotropia that could be corrected with glasses, either completely (fully accommodative) or partially (partially accommodative). In our analyses, fully and partially accommodative esotropia were combined as “accommodative esotropia”. We classified esotropia that did not meet the criteria for congenital or accommodative esotropia as “other esotropia”. “Exotropia” included all exotropia diagnoses. We classified children with any orbital nerve paresis as having “other strabismus”.

Ascertainment of Perinatal Characteristics

Using the Medical Birth Register, we obtained information on mode of delivery, birth weight, gestational age at birth, head circumference, Apgar score at 5 minutes, single/multiple gestation, neonatal septicemia, neonatal asphyxia, maternal pre-eclampsia, and parental ages. We searched the National Patient Register for ICD-10 codes for asphyxia (I11-69, J, O68, P20-29, R09) and septicemia (P36) in the child up to 20 days after delivery. We also searched for congenital abnormality diagnoses (ICD-10 codes Q00-Q99) at any age. We grouped congenital abnormalities based on proximity to the eyes, ranked as follows: 1) chromosomal abnormalities; 2) malformations of the head and neck (not including cleft palate/lip); 3) other malformations (including cleft palate/lip); and 4) no malformations. Children with multiple abnormalities were classified based on the diagnosis ranking highest in the above list.

Data Analysis

We used log-linear binomial regression to estimate risk ratios (referred to hereafter as relative risks) associated with individual perinatal risk factors for strabismus overall. All estimates were adjusted for birth year to take into account differences in follow-up time according to birth year. We also examined the effect of adjusting for birth weight and restricting our analyses to children without congenital abnormalities. In addition to this, we then performed a multivariable analysis

including only children without congenital abnormalities; to be conservative, we initially included in this analysis birth weight, birth year, and variables with $P < 0.10$ in the individual variable analyses after adjustment for birth year and birth weight and exclusion of children with congenital abnormalities. Using a backward elimination procedure, we then reduced the multivariable model to include only those variables that were independent risk factors ($P < 0.05$) for strabismus overall.

We performed additional multivariable analyses adjusting for the highest social class of the household (academics/employed requiring highly specialized skills, employed requiring medium skills, skilled labor, students, unskilled labor, and unemployed), daily maternal smoking dose (0, 0.1-4.9, 5-9.9, 10+ cigarettes per day) and weekly maternal alcohol consumption (0, 0.1-0.9, 1-2.9, 3-4.9, 5+ 12-gram units of alcohol per week) during pregnancy. This was done primarily to evaluate whether these risk factors were confounders of the observed perinatal risk factor-strabismus associations,(21) but also to evaluate whether confounding was introduced by adjusting for birth weight in analyses where birth weight could be regarded as an intermediate variable.(22)

We used polytomous logistic regression to compare risk factors for strabismus subtypes. To ensure that we did not overlook variables of importance to specific subtypes, risk factors with $P < 0.2$ in the analyses of strabismus overall with adjustment for birth year and birth weight and exclusion of congenital abnormalities were considered in the comparison of strabismus subtypes. We decided a priori to adjust strabismus subtype analyses for birth weight.

We used SAS Version 9.2 (SAS Institute, Inc., Cary, NC, USA) for data analysis.

Results

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Evaluation of 5655 ophthalmologic records yielded 1321 strabismus cases. One child with strabismus caused by trauma was excluded, leaving 1320 cases for analysis in a cohort of 96 842 children. We first present associations between perinatal risk factors and risk of strabismus overall, followed by the results of separate analyses for congenital esotropia, accommodative esotropia, all exotropia, and other strabismus.

Figure 1a shows the association between birth weight and any strabismus, adjusted only for birth year. Children with birth weights below 2500g had an increased risk of strabismus, compared with children with birth weights above 2500g ($P<0.001$). Additional adjustment for gestational age affected the risk estimates for birth weight very little ($P=0.001$) (Figure 1b).

Figure 1c shows the association between gestational age and any strabismus, adjusted only for birth year; children born before week 37 of gestation had an appreciably higher risk of strabismus than children born in weeks 37-41 ($P<0.001$). However, after adjusting for birth weight, the association with gestational age diminished markedly ($P=0.05$) (Figure 1d)

Table 1 presents associations between perinatal characteristics and strabismus overall. Relative risk estimates are adjusted for 1) birth year only, 2) birth year and birth weight, and 3) birth year and birth weight in children with no malformations or chromosomal abnormalities. When only adjusting for birth year, asphyxia, a low Apgar score, Cesarean delivery, small and large head circumferences, maternal pre-eclampsia, multiple gestation, and neonatal septicemia were all associated with strabismus. We obtained similar results when we further adjusted the estimates for social class and maternal smoking and alcohol consumption during pregnancy (data not shown).

After additional adjustment for birth weight, children with neonatal asphyxia remained at elevated risk of strabismus (Table 1). Similarly, children born by Cesarean section had an increased risk of strabismus compared with children born vaginally (Table 1). Estimate magnitudes for neonatal asphyxia and Cesarean section remained similar when children with congenital abnormalities were excluded from the analyses (Table 1).

Compared with children born with a head circumference of 34-37 cm, children with larger head circumferences had a 36% (95% CI 11%-69%) higher risk of strabismus, after additional adjustment for birth weight. The risks associated with a head circumference of 33 cm or less remained elevated, although more modestly so, after adjustment for birth weight. Our head circumference estimates did not change further when children with congenital abnormalities were excluded from the analyses (Table 1).

To explore the robustness of the above results, we performed an additional multivariable analysis (with backward elimination of variables), initially including the variables Cesarean delivery, maternal pre-eclampsia, head circumference, gestational age and birth weight, in children without congenital abnormalities (results not shown). Using this approach, we also found that only birth weight ($P_{\text{homogeneity}}=0.001$), gestational age ($P_{\text{homogeneity}}=0.05$), and head circumference ($P_{\text{homogeneity}}=0.02$) were associated with strabismus risk. Compared with children weighing 3000-3500 g at birth, children weighing less than 2000g had a 42% (95% CI -15%-135%) increased risk of strabismus, while children weighing 2000-2500g had a 74% (95% CI 28%-137%) increased risk of strabismus. Compared with children born in gestational weeks 37-42, children born in week 32 or earlier had a 19% (95% CI -34%-114%) increased risk of strabismus, while children born in weeks 33-36 had a 39% (95% CI 8%-80%) increased risk of strabismus. Children born post-term had an 18% (95% CI -2%-34%) decreased risk of strabismus.

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Table 2 presents associations between congenital abnormalities and risk of strabismus. After adjustment for birth weight, children with abnormalities had a 57%-655% increased risk of strabismus compared with children with no abnormalities, depending on the abnormality.

Table 3 presents associations between perinatal risk factors and esotropia (n=1048) and exotropia (n=183) separately. All estimates are adjusted for birth weight. Congenital abnormalities of all types were more strongly associated with exotropia than esotropia ($P<0.001$). In fact, 40 (22%) of the 183 exotropia cases also had one or more congenital abnormalities, compared with 12% of esotropia cases. The most frequent abnormalities among the 30 exotropic children with malformations in only a single organ system were musculo-skeletal (n=9), facial (n=7), and malformations of the nervous system (n=4).

Compared with children delivered vaginally, children born by Cesarean section had no increased risk of esotropia, while their risk of exotropia was increased by 65% (95% CI 16%-134%). Maternal pre-eclampsia, neonatal septicemia, gestational age at birth, and head circumference did not affect the risks of esotropia and exotropia differently (Table 3).

Table 4 presents associations between perinatal risk factors and esotropia subtypes. Compared with children with no congenital abnormalities, children with chromosomal abnormalities or syndromes had an elevated risk of all three subtypes of esotropia. Children with malformations of the head and neck and children with other malformations had elevated risks of congenital esotropia and other esotropia, but not of accommodative esotropia. Birth weight was the only other variable that affected esotropia risk differently depending on subtype ($p=0.04$), with congenital esotropia yielding the highest relative risk estimates for low birth weight.

We could not obtain ophthalmologic records for 3128 children. However, these children did not differ from children with available records with respect to the distribution of birth year, birth weight, or gestational age at birth (data not shown), and participating and non-participating ophthalmologists did not differ in terms of the numbers of records we were attempting to access or the region of the country in which they practiced (data not shown). Children with missing records were excluded from our primary analyses. However, we also performed an alternate analysis where these children were considered strabismus-free. This had very little effect on the effect estimates and did not change our conclusions (data not shown).

Discussion

In this population-based cohort study, strabismus risk was associated with low birth weight, low gestational age at birth, large head circumference and congenital abnormalities. Congenital abnormalities were more strongly associated with exotropia than with esotropia; of particular note, as many as 22% of exotropic children also had a malformation or chromosomal abnormality. Children born by Cesarean section had an increased risk of exotropia, while their risk of esotropia was unaffected.

The inverse association we observed between strabismus and birth weight is in line with previous findings in a cohort of children born in 1959-1966.⁽³⁾ Other studies have reported strabismus prevalences of 12%-36% in very low birth weight children (birth weight less than 1500 g),^(7;9;10;12) compared with 2%-6% in the general pediatric population.⁽¹⁻⁶⁾ The Sydney Myopia Study, a large population-based cross-sectional study of ophthalmologic conditions in young children (n=1739, 48 with strabismus when assessed at 6-7 years of age), found that children weighing less than 2500 g at birth were 3.5 times more likely than children who were greater than 2500 g at birth to have any type of strabismus;⁽¹³⁾ modest low birth weight (1500-2499 g) increased the risk of any strabismus at 6-7 years 3.7-fold, compared with normal birth

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weight (≥ 2500 g).(14) Compared with children of normal birth weight, we found a 2-fold increased risk of strabismus both in children weighing less than 2000 g and in those weighing 2000-2500 g at birth. The large size of our study cohort resulted in robust estimates, with an upper confidence limit of less than 2.6 for both estimates. In contrast to our findings that low birth weight (< 2500 g) increased the risk of esotropia slightly more than 2-fold and the risk of exotropia only modestly (approximately 20-50%), the Sydney Myopia Study found that low birth weight children were 3.4 times more likely to be esotropic and 2.5 times more likely to be exotropic than children with normal birth weights, although both estimates were based on very small numbers of children.(13) Major and colleagues reported an unadjusted odds ratio for congenital esotropia of 5.9 for children weighing less than 2500 g,(11) which compares favorably with our relative risks of 2.66 and 3.58 for children weighing less than 2000 g and 2000-2499 g, respectively.

Several groups have reported an association between prematurity and an increased risk of strabismus,(3;11;13-15) but only one group adjusted their gestational age estimate for birth weight, reporting a residual effect of gestational age after adjustment.(3) In their report on vision problems in 7538 7-year-old children from the Avon Longitudinal Study of Parents and Children (ALSPAC), Williams and colleagues examined the effects of gestational age alone and birth weight adjusted for gestational age.(6) They found that prematurity (gestation < 37 weeks) increased the risk of “clinically significant convergent strabismus” (esotropia) by roughly 2.5-fold, but did not affect the risk of “clinically significant divergent strabismus” (exotropia), whereas intrauterine growth retardation (birth weight adjusted for gestational age more than 2 standard deviations lower than mean) increased the risk of exotropia 4.3-4.5 times but had no effect on the risk of esotropia.(6) In our analyses, the influence of birth weight appeared to explain most of the effect of gestational age, whereas adjusting for gestational age did not change the association between birth weight and strabismus.

We found very strong associations between several groups of congenital abnormalities and strabismus, whereas previous studies have only found associations between specific abnormalities and strabismus.(23-27) In our study, congenital abnormalities were more strongly associated with exotropia than with esotropia, with 22% of exotropic children also having one or more abnormalities. Similarly, Izquierdo and colleagues reported a 5.6:1 exotropia:esotropia ratio in 573 subjects with Marfan syndrome,(27) although esotropia is more common than exotropia in Western countries.(3;6;28) and Hunter and Ellis reported a higher association of genetic disorders particularly with infantile constant exotropia.(29) The large difference in the effect of congenital abnormalities on exotropia versus esotropia risk found in our study suggests that the pathogenesis of exotropia differs from that of esotropia. In support of this view, we also found that Cesarean delivery affected the risk of strabismus subtypes differently, increasing the risk of exotropia but not esotropia.

We found an association between large head circumference and strabismus risk, even after excluding children with congenital malformations. A large head circumference can point to both chromosomal abnormalities and conditions such as hydrocephalus, which could explain our findings. We found a similar association with small head circumference. Small neonatal head circumference has previously been described as a predictor of poor mental and motor development (30) and may at least in part explain the observed association.

Danish general practitioners were responsible for recruiting pregnant women for the DNBC; 64% of general practitioners nationwide participated in recruitment activities. More than 60% of eligible pregnant women receiving prenatal care from participating general practitioners enrolled in the DNBC, with the result that the DNBC included roughly 30% of all children born in Denmark during the enrollment period. Since neither a physician's decision to recruit women

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for the DNBC nor a pregnant woman’s decision to participate in the cohort were likely to have been related to subsequent birth characteristics, our results are unlikely to have been subject to selection bias. Furthermore, a 2006 study concluded that although DNBC women were marginally healthier than the background population, any bias of risk estimates due to a “healthy woman” phenomenon would be small.(19)

We were unable to retrieve ophthalmologic records for 36% of children who had been seen by an ophthalmologist and could have been diagnosed with strabismus. However, children with missing records were similar to those whose records we evaluated with respect to birth year, birth weight, and gestational age at birth. Furthermore, missingness was almost exclusively explained by OPP refusal to participate or by our inability to reach certain OPPs. Given the structure of the Danish health care system, we find it difficult to identify a mechanism whereby such non-participation could seriously bias our results.

Our study had several strengths. It was based on a large population-based cohort, which gave us the ability to study strabismus subtypes. Review of ophthalmologic records was performed by personnel specifically trained in strabismus classification, providing an accurate classification of strabismus. The use of national registers to which reporting is mandatory helped to ensure complete strabismus case ascertainment. Furthermore, health care in Denmark is free, allowing all residents equal access to medical care and ensuring that most strabismus cases get diagnosed. Information on potential perinatal risk factors was registered in national registers by attending midwives prior to, and independent, of strabismus diagnosis, minimizing potential recall bias.

To conclude, in a large population-based cohort study, we identified low birth weight, prematurity, large head circumference, and congenital abnormalities as risk factors for strabismus overall. Both congenital abnormalities and Cesarean delivery influenced the risk of

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For Review Only

Figure Legends

Figure 1.

Relative risk of strabismus according to birth weight and gestational age in a cohort of 96 842

Danish children born between 1996 and 2003. Birth weight categories are: <2000g, 2000-2499g,

2500-2999g, 3000-3499g (reference), 3500-3999g, 4000-4499g, and ≥ 4500 g. Gestational age

categories are: weeks <33, weeks 33-36, weeks 37-41 (reference), and weeks ≥ 42 .

a) Relative risk of strabismus according to birth weight.

b) Relative risk of strabismus according to birth weight, adjusted for gestational age at birth.

c) Relative risk of strabismus according to gestational age at birth.

d) Relative risk of strabismus according to gestational age at birth, adjusted for birth weight.

References

- (1) McNeil NL. Patterns on visual defects in children. *Br J Ophthalmol* 1955; **39**: 688-701.
- (2) Frandsen AD. Some results from a clinical-statistical survey on strabismus among Copenhagen children. *Acta Ophthalmol* 1958; **36**: 488-98.
- (3) Chew E, Remaley NA, Tamboli A, Zhao J, Podgor MJ, Klebanoff M. Risk factors for esotropia and exotropia. *Arch Ophthalmol* 1994; **112**: 1349-55.
- (4) Nordl w W. Squint - The frequency of onset at different ages, and the incidence of some associated defects in a Swedish population. *Acta Ophthalmol (Copenh)* 1964; **42**: 1015-37.
- (5) Graham PA. Epidemiology of strabismus. *Br J Ophthalmol* 1974; **58**: 224-31.
- (6) Williams C, Northstone K, Howard M, Harvey I, Harrad RA, Sparrow JM. Prevalence and risk factors for common vision problems in children: data from the ALSPAC study. *Br J Ophthalmol* 2008; **92**: 959-64.
- (7) Keith CG, Kitchen WH. Ocular morbidity in infants of very low birth weight. *Br J Ophthalmol* 1983; **67**: 302-5.
- (8) Powls A, Botting N, Cooke RW, Stephenson G, Marlow N. Visual impairment in very low birthweight children. *Arch Dis Child Fetal Neonatal Ed* 1997; **76**: F82-F87.
- (9) Bremer DL, Palmer EA, Fellows RR, et al. Strabismus in premature infants in the first year of life. Cryotherapy for Retinopathy of Prematurity Cooperative Group. *Arch Ophthalmol* 1998; **116**: 329-33.
- (10) Holmstrom G, el AM, Kugelberg U. Ophthalmological follow up of preterm infants: a population based, prospective study of visual acuity and strabismus. *Br J Ophthalmol* 1999; **83**: 143-50.
- (11) Major A, Maples WC, Toomey S, DeRosier W, Gahn D. Variables associated with the incidence of infantile esotropia. *Optometry* 2007; **78**: 534-41.
- (12) Lindqvist S, Vik T, Indredavik MS, Skranes J, Brubakk AM. Eye movements and binocular function in low birthweight teenagers. *Acta Ophthalmol* 2008; **86**: 265-74.
- (13) Robaei D, Rose K, Kifley A, et al. Factors associated with childhood strabismus. *Ophthalmology* 2006; **113**: 1146-53.
- (14) Robaei D, Kifley A, Gole G, et al. The impact of modest prematurity on visual function at age 6 years. *Arch Ophthalmol* 2006; **124**: 871-7.
- (15) Pennefather PM, Clarke MP, Strong NP, Cottrell DG, Dutton J, Tin W. Risk factors for strabismus in children born before 32 weeks' gestation. *Br J Ophthalmol* 1999; **83**: 514-8.
- (16) Holmstrom G, Larsson E. Long-term follow-up of visual functions in prematurely born children--a prospective population-based study up to 10 years of age. *J AAPOS* 2008; **12**: 157-62.
- (17) Mohnney BG, Erie JC, Hodge DO, Jacobsen SJ. Congenital esotropia in Olmsted County, Minnesota. *Ophthalmology* 1998; **105**: 846-50.

- (18) Olsen J, Melbye M, Olsen SF, et al. The Danish National Birth Cohort--its background, structure and aim. *Scand J Public Health* 2001; **29**: 300-7.
- (19) Nohr EA, Frydenberg M, Henriksen TB, Olsen J. Does low participation in cohort studies induce bias? *Epidemiology* 2006; **17**: 413-8.
- (20) Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999; **46**: 263-8.
- (21) Torp-Pedersen T, Boyd H, Poulsen G, Haargaard B, Wohlfahrt J, Holmes J, Melbye M. In utero exposure to smoking, alcohol, coffee and tea and risk of strabismus. *Am J Epidemiol*. In press 2010.
- (22) Cole SR, Hernan MA. Fallibility in estimating direct effects. *Int J Epidemiol* 2002; **31**: 163-5.
- (23) Creavin AL, Brown RD. Ophthalmic abnormalities in children with Down syndrome. *J Pediatr Ophthalmol Strabismus* 2009; **46**: 76-82.
- (24) Casteels I, Casaer P, Gewillig M, Swillen A, Devriendt K. Ocular findings in children with a microdeletion in chromosome 22q11.2. *Eur J Pediatr* 2008; **167**: 751-5.
- (25) Kuchukhidze G, Rauchenzauner M, Gotwald T, Janecke A, Trinkla E. Hypoplasia of deep cerebellar nuclei in joubert syndrome. *Pediatr Neurol* 2009; **40**: 474-6.
- (26) Mansour AM, Bitar FF, Traboulsi EI, et al. Ocular pathology in congenital heart disease. *Eye* 2005; **19**: 29-34.
- (27) Izquierdo NJ, Traboulsi EI, Enger C, Maumenee IH. Strabismus in the Marfan syndrome. *Am J Ophthalmol* 1994; **117**: 632-5.
- (28) Mohny BG, Greenberg AE, Diehl NN. Age at strabismus diagnosis in an incidence cohort of children. *Am J Ophthalmol* 2007; **144**: 467-9.
- (29) Hunter DG, Ellis FJ. Prevalence of Systemic and Ocular Disease in Infantile Exotropia. *Ophthalmology* 1999; **106**: 1951-1956
- (30) Badr LK, Bookheimer S, Purdy I, Deeb M. Predictors of neurodevelopmental outcome for preterm infants with brain injury: MRI, medical and environmental factors. *Early Hum Dev* 2009; **85**: 279-84.

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Table 1. Relative risk of strabismus according to birth characteristics in a cohort of 96,842 Danish children born between 1996 and 2003.

Birth characteristics		Number of cases (n=1320)	Relative risk (95% confidence interval)		
			Adjusted for birth year	Adjusted for birth weight and birth year Congenital abnormalities included	Congenital abnormalities excluded
Asphyxia	No	1193	1 (ref)	1 (ref)	1 (ref)
	Yes	127	1.50 (1.25-1.80)	1.22 (1.01-1.49)	1.15 (0.96-1.63)
	<i>P_{homogeneity}</i>		<i>P=0.001</i>	<i>P=0.05</i>	<i>P=0.23</i>
Apgar score (5 min)	10	1181	1 (ref)	1 (ref)	1 (ref)
	7-9	110	1.20 (0.99-1.46)	1.10 (0.90-1.34)	1.05 (0.84-1.30)
	0-6	17	1.72 (1.07-2.76)	1.44 (0.89-2.33)	1.39 (0.79-1.26)
	Missing	12	-	-	-
	<i>P_{homogeneity}</i>		<i>P=0.03</i>	<i>P=0.25</i>	<i>P=0.53</i>
Cesarean Delivery	No	1045	1 (ref)	1 (ref)	1 (ref)
	Yes	275	1.35 (1.18-1.53)	1.17 (1.01-1.34)	1.15 (0.99-1.34)
	<i>P_{homogeneity}</i>		<i>P=0.001</i>	<i>P=0.04</i>	<i>P=0.07</i>
Head circumference (cm)	<30	31	2.28 (1.60-3.24)	1.18 (0.71-1.96)	1.34 (0.76-2.36)
	31-33	212	1.46 (1.26-1.70)	1.11 (0.93-1.33)	1.09 (0.90-1.32)
	34-37	896	1 (ref)	1 (ref)	1 (ref)
	38+	120	1.31 (1.09-1.59)	1.36 (1.11-1.69)	1.39 (1.11-1.74)
	Missing	61	-	-	-
	<i>P_{homogeneity}</i>		<i>P<0.001</i>	<i>P=0.03</i>	<i>P=0.03</i>
Maternal age (years)	< 25	127	1.00 (0.83-1.16)	0.98 (0.81-1.19)	0.95 (0.77-1.17)
	25-30	504	1 (ref)	1 (ref)	1 (ref)
	30-35	494	0.99 (0.88-1.12)	1.00 (0.88-1.13)	1.00 (0.88-1.14)
	35+	195	0.98 (0.83-1.16)	0.97 (0.82-1.14)	0.97 (0.81-1.16)
	<i>P_{homogeneity}</i>		<i>P=1.00</i>	<i>P=0.98</i>	<i>P=0.95</i>
Maternal pre-eclampsia	No	1246	1 (ref)	1 (ref)	1 (ref)
	Yes	74	1.54 (1.20-1.94)	1.26 (0.98-1.59)	1.27 (0.98-1.64)
	<i>P_{homogeneity}</i>		<i>P=0.001</i>	<i>P=0.08</i>	<i>P=0.09</i>
Multiple gestation	No	1246	1 (ref)	1 (ref)	1 (ref)
	Yes	74	1.39 (1.07-1.71)	0.85 (0.66-1.11)	0.95 (0.72-1.26)
	<i>P_{homogeneity}</i>		<i>P=0.01</i>	<i>P=0.23</i>	<i>P=0.73</i>
Neonatal Septicemia	No	1286	1 (ref)	1 (ref)	1 (ref)
	Yes	34	1.64 (1.17-2.30)	1.40 (0.99-1.97)	1.34 (0.90-1.99)
	<i>P_{homogeneity}</i>		<i>P=0.01</i>	<i>P=0.07</i>	<i>P=0.17</i>
Paternal age (years)	< 25	57	1.04 (0.79-1.37)	1.01 (0.77-1.33)	1.02 (0.76-1.36)
	25-29	333	0.99 (0.86-1.14)	0.98 (0.85-1.12)	1.02 (0.88-1.18)
	30-34	500	1 (ref)	1 (ref)	1 (ref)
	35-39	301	1.13 (0.98-1.30)	1.12 (0.98-1.30)	1.08 (0.93-1.26)
	40+	105	0.99 (0.81-1.22)	0.97 (0.79-1.20)	1.01 (0.80-1.26)
	Missing	24	-	-	-
	<i>P_{homogeneity}</i>		<i>P=0.45</i>	<i>P=0.43</i>	<i>P=0.91</i>

Table 2. Relative risk of strabismus according to type of congenital abnormality in a cohort of 96 842 Danish children born between 1996 and 2003

Congenital abnormalities	Number of cases (n=1320)	Relative risk (95% confidence interval)	
		Adjusted for birth year only	Adjusted for birth weight and birth year
Chromosomal aberrations/syndromes ¹	26	7.66 (5.30-11.1)	6.55 (4.55-9.50)
Head and neck malformations ²	36	4.07 (2.95-5.62)	3.91 (2.83-5.40)
Other malformations ³	116	1.62 (1.34-1.96)	1.57 (1.29-1.89)
No malformations	1142	1 (ref)	1 (ref)
<i>P_{homogeneity}</i>		<i>P<0.001</i>	<i>P<0.001</i>
1 ICD 10 codes Q86-87, Q90-99			
2 ICD 10 codes Q00-19, Q30-31, Q35-38			
3 ICD 10 codes Q20-29, Q32-85, Q88-89			

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Table 3. Relative risks of esotropia and exotropia according to birth characteristics in a cohort of 96 842 Danish children born between 1996 and 2003

Birth characteristics		All esotropia		All exotropia		Test for difference between relative risks for esotropia and exotropia
		Number of cases (n=1048)	Relative risk* (95% confidence interval)	Number of cases (n=183)	Relative risk* (95% confidence interval)	
Birth weight (g)	< 2000	41	2.20 (1.60-3.05)	5	1.52 (0.61-3.81)	<i>P</i> =0.73
	2000-2499	65	2.35 (1.80-3.07)	6	1.23 (0.53-2.86)	
	2500-2999	126	1.29 (1.04-1.58)	22	1.26 (0.77-2.08)	
	3000-3499	287	1 (ref)	51	1 (ref)	
	3500-3999	296	0.85 (0.72-0.99)	59	0.95 (0.65-1.38)	
	4000-4499	171	0.97 (0.80-1.17)	30	0.95 (0.61-1.49)	
	4500+	54	1.21 (0.91-1.61)	1	1.12 (0.55-2.28)	
	Missing	8	-	1	-	
	<i>P_{homogeneity}</i>		<i>P</i> <0.001		<i>P</i> =0.875	
Cesarean delivery	No	840	1 (ref)	138	1 (ref)	<i>P</i> =0.03
	Yes	208	1.06 (0.91-1.25)	45	1.65 (1.16-2.34)	
	<i>P_{homogeneity}</i>		<i>P</i> =0.44		<i>P</i> =0.01	
Congenital abnormalities	None	928	1 (ref)	143	1 (ref)	<i>P</i> <0.001
	Other	81	1.34 (1.06-1.68)	20	2.24 (1.40-3.57)	
	Head / neck	21	2.80 (1.83-4.28)	13	11.7 (6.67-20.7)	
	Chrom / syn**	18	5.47 (3.48-8.60)	7	16.1 (7.51-34.6)	
	<i>P_{homogeneity}</i>		<i>P</i> <0.001		<i>P</i> <0.001	
Gestational age at birth (weeks)	< 33	28	1.21 (0.69-2.12)	1	0.13 (0.01-1.17)	<i>P</i> =0.16
	33-36.9	100	1.39 (1.07-1.81)	10	0.70 (0.32-1.53)	
	37-41.9	841	1 (ref)	156	1 (ref)	
	≥ 42	79	0.81 (0.65-1.03)	16	0.90 (0.53-1.52)	
	<i>P_{homogeneity}</i>		<i>P</i> =0.03		<i>P</i> =0.19	
Head circumference (cm)	≤ 30	27	1.41 (0.81-2.46)	1	0.13 (0.01-1.27)	<i>P</i> =0.17
	31-33	172	1.16 (0.95-1.41)	23	0.84 (0.50-1.42)	
	34-37	696	1 (ref)	137	1 (ref)	
	≥ 38	100	1.42 (1.13-1.79)	15	1.08 (0.60-1.93)	
	Missing	53	-	7	-	
	<i>P_{homogeneity}</i>		<i>P</i> =0.01		<i>P</i> =0.24	
Maternal pre-eclampsia	No	991	1 (ref)	171	1 (ref)	<i>P</i> =0.25
	Yes	57	1.17 (0.89-1.54)	12	1.73 (0.95-3.14)	
	<i>P_{homogeneity}</i>		<i>P</i> =0.28		<i>P</i> =0.10	
Neonatal septicemia	No	1019	1 (ref)	179	1 (ref)	<i>P</i> =0.81
	Yes	29	1.48 (1.02-2.15)	4	1.29 (0.47-3.54)	
	<i>P_{homogeneity}</i>		<i>P</i> =0.05		<i>P</i> =0.63	

* Adjusted for birth year and birth weight

** Chromosomal aberrations and syndromes

Table 4. Relative risks for esotropia subtypes according to birth characteristics in a cohort of 96 842 Danish children born between 1996 and 2003.

Birth characteristics	Congenital esotropia		Accommodative esotropia		Other esotropia		Test for difference between esotropia subtype relative risks
	Number of cases (n=217)	Relative risk* (95% confidence interval)	Number of cases (n=432)	Relative risk* (95% confidence interval)	Number of cases (n=399)	Relative risk* (95% confidence interval)	
Birth weight (g)	< 2000	10 2.66 (1.36-5.20)	16 2.06 (1.22-3.45)	15 2.12 (1.24-3.63)			P=0.04
	2000-2499	20 3.58 (2.16-5.95)	17 1.47 (0.89-2.45)	28 2.66 (1.76-4.02)			
	2500-2999	30 1.51 (0.97-2.35)	57 1.39 (1.02-1.91)	39 1.05 (0.73-1.51)			
	3000-3499	47 1 (ref)	115 1 (ref)	134 1 (ref)			
	3500-3999	40 0.67 (0.45-1.68)	80 0.79 (0.61-1.01)	51 1.01 (0.78-1.30)			
	4000-4499	11 1.12 (0.75-1.68)	23 1.08 (0.82-1.44)	20 0.76 (0.55-1.06)			
	4500 +	58 1.22 (0.64-2.32)	120 1.23 (0.79-1.92)	109 1.18 (0.73-1.90)			
	Missing	1 -	4 -	3 -			
	<i>Phomogeneity</i>	<i>P<0.001</i>	<i>P=0.001</i>	<i>P<0.001</i>			
Caesarean delivery	No	170 1 (ref)	348 1 (ref)	322 1 (ref)			P=0.91
	Yes	47 1.08 (0.77-1.53)	84 1.10 (0.86-1.41)	77 1.02 (0.78-1.33)			
	<i>Phomogeneity</i>	<i>P=0.65</i>	<i>P=0.46</i>	<i>P=0.90</i>			
Congenital abnormalities	None	186 1 (ref)	400 1 (ref)	342 1 (ref)			P=0.002
	Other	20 1.56 (0.98-2.48)	19 0.72 (0.46-1.15)	42 1.81 (1.31-2.51)			
	Head/neck	5 3.05 (1.26-7.41)	3 0.91 (0.29-2.82)	13 4.57 (2.64-7.93)			
	Chrom/syn*	6 7.43 (3.29-16.8)	10 6.80 (3.63-12.7)	2 1.56 (0.39-6.24)			
	<i>Phomogeneity</i>	<i>P<0.001</i>	<i>P<0.001</i>	<i>P<0.001</i>			
Gestational age at birth (weeks)	< 33	8 1.44 (0.48-4.29)	7 0.64 (0.24-1.72)	13 1.88 (0.77-4.55)			P=0.64
	33-36.9	23 1.11 (0.64-1.95)	39 1.44 (0.95-2.19)	38 1.54 (1.00-2.37)			
	37-41.9	172 1 (ref)	352 1 (ref)	317 1 (ref)			
	≥ 42	14 0.71 (0.41-1.23)	34 0.82 (0.58-1.18)	31 0.86 (0.59-1.25)			
	<i>Phomogeneity</i>	<i>P=0.55</i>	<i>P=0.08</i>	<i>P=0.18</i>			
Head circumference (cm)	≤ 30	6 1.41 (0.45-4.42)	12 1.45 (0.61-3.47)	9 1.37 (0.54-3.49)			P=0.93
	31-33	43 1.28 (0.84-1.96)	71 1.25 (0.93-1.70)	58 0.99 (0.70-1.38)			
	34-37	132 1 (ref)	293 1 (ref)	271 1 (ref)			
	≥ 38	22 1.58 (0.95-2.64)	41 1.30 (0.91-1.87)	37 1.47 (1.00-2.16)			
	Missing	14 -	15 -	24 -			
	<i>Phomogeneity</i>	<i>P=0.02</i>	<i>P=0.25</i>	<i>P=0.25</i>			
Maternal pre-eclampsia	No	205 1 (ref)	406 1 (ref)	380 1 (ref)			P= 0.24
	Yes	12 1.13 (0.62-2.04)	26 1.34 (0.88-2.04)	19 1.01 (0.63-1.64)			
	<i>Phomogeneity</i>	<i>P=0.70</i>	<i>P=0.19</i>	<i>P=0.95</i>			
Neonatal septicemia	No	208 1 (ref)	422 1 (ref)	389 1 (ref)			P=0.51
	Yes	9 2.12 (1.07-4.20)	10 1.26 (0.67-2.39)	10 1.34 (0.71-2.54)			
	<i>Phomogeneity</i>	<i>P=0.05</i>	<i>P=0.49</i>	<i>P=0.39</i>			

* Adjusted for birth year and birth weight

** Chromosomal aberrations and syndromes

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Key Messages

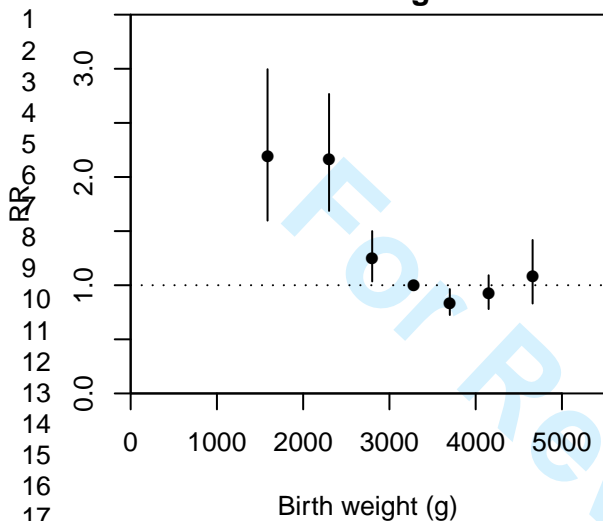
In this population-based cohort study, low birth weight, prematurity, large head circumference and congenital abnormalities were associated with risk of strabismus overall.

Congenital abnormalities were much more strongly associated with exotropia than with esotropia. Given the substantial proportion of exotropic children with congenital abnormalities, a large angle exotropia in an infant should alert physicians to the possibility of a genetic disorder.

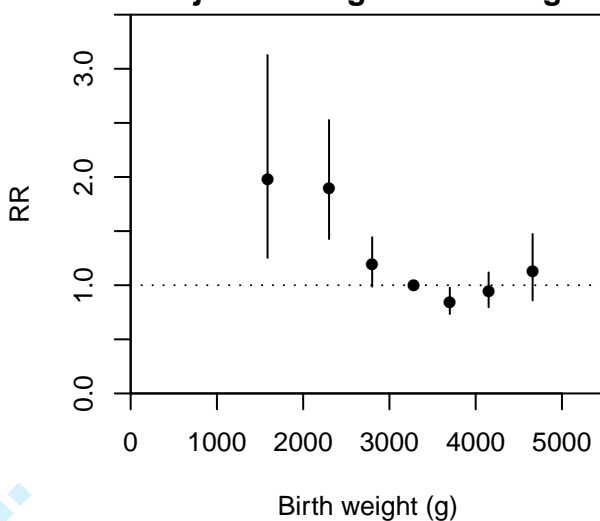
Children born by Cesarean section had an increased risk of exotropia, while their risk of esotropia was unaffected.

The differences in the effects of congenital abnormalities and Cesarean delivery on esotropia and exotropia suggest that strabismus subtypes have different underlying etiologies.

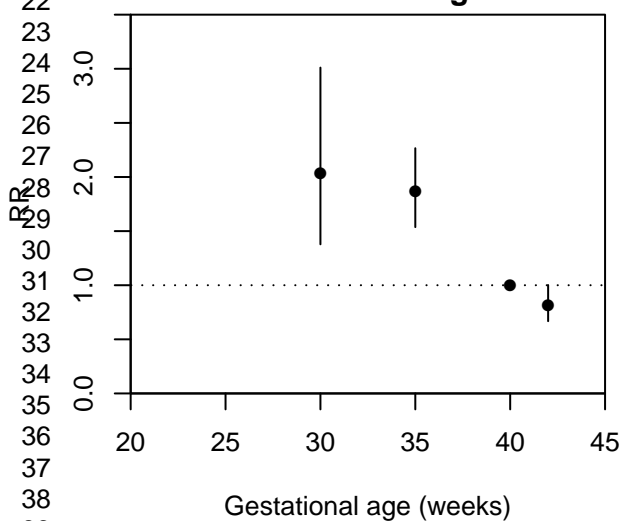
a)
Birth weight



b)
Birth weight
adjusted for gestational age



c)
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