Effect of Gestational Age and Birth Weight on the Risk of Strabismus Among Premature Infants

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IMPORTANCE Strabismus causes irreversible vision loss if not detected and treated early. It is unclear whether birth weight (BW) and gestational age (GA) are risk factors for strabismus.

OBJECTIVE To estimate the effect of BW and GA on the likelihood of premature infants developing strabismus.

DESIGN, SETTING, AND PARTICIPANTS In this longitudinal cohort analysis, we monitored a group of premature children from birth to determine the proportion that developed strabismus and the timing of the first strabismus diagnosis. Multivariable Cox regression analyses assessed the relationships of BW and GA with the development of strabismus. Regression models were adjusted for other risk factors for strabismus, sociodemographic factors, and ocular comorbidities. The analysis included 38 055 otherwise healthy children born prematurely who were enrolled for more than 6 months in a nationwide US managed care network between 2001 and 2011 in communities throughout the United States.

EXPOSURES Birth weight less than 2000 g or GA of 32 weeks or less.

MAIN OUTCOMES AND MEASURES Hazard ratios (HRs) for strabismus with 95% CIs.

RESULTS Of 38 055 otherwise healthy children who were born prematurely, 583 received a diagnosis of strabismus later in life. The cumulative incidence of strabismus was 3.0% at 5 years. Controlling for GA and other covariates, infants born with BW less than 2000 g had a 61% increased hazard (HR, 1.61; 95% CI, 1.22-2.13) of developing strabismus. Controlling for BW and other covariates, there was no significant association between strabismus and GA (HR, 0.98; 95% CI, 0.69-1.38). Among premature infants with BW of less than 2000 g, a GA of 32 weeks or less conveyed no additional increased risk for developing strabismus relative to infants born after 32 weeks (HR, 1.27; 95% CI, 0.86-1.88). In contrast, among infants with a GA of 32 weeks or less, BW of less than 2000 g conveyed a 14-fold increase in the risk of strabismus relative to BW of 2000 g or more (HR, 14.39; 95% CI, 1.99-104.14).

CONCLUSIONS AND RELEVANCE Independent of GA, very low BW conferred a large increase in strabismus risk among premature infants. In contrast, independent of BW, GA did not significantly affect the risk of strabismus. Updates to existing guidelines in the pediatric and ophthalmic literature should be considered, highlighting the importance of BW rather than GA and alerting clinicians about the need for careful monitoring of premature infants with low BW for strabismus.
Strabismus is a common childhood ocular condition estimated to affect 2% to 4% of children between the ages of 6 months and 5 years. If left untreated, children with strabismus are at increased risk for amblyopia. Strabismus can have a dramatic effect on the quality of well-being, affecting self-image and social interactions of preschool and early school age children. Studies have found that intervening early to correct strabismus results in improved best-corrected visual acuity, a reduced need for later surgical interventions, and reduced societal costs.

Well-recognized risk factors for strabismus include anisometropia and refractive error, genetics, older age of parents, maternal cigarette smoking during pregnancy, neurodevelopmental impairment, low Apgar (appearance, pulse, grimace, activity, and respiration) scores, craniofacial and chromosomal abnormalities, in utero toxin exposure, retinopathy of prematurity (ROP), and cesarean delivery. For children who are born prematurely, there is debate in the literature regarding 2 other potential risk factors: birth weight (BW) and gestational age (GA). Studies found that both BW and GA were independent significant risk factors for strabismus, and another study noted that only infants with both low BW and GA were at increased risk. Two studies looked specifically at premature infants. Bremer and colleagues monitored 2449 premature infants but came to disparate conclusions regarding the effect of BW and GA on strabismus risk. Of these, 3 studies found that both BW and GA were independent significant risk factors for strabismus, 2 studies found that only GA was significant, and another study noted that only infants with both low BW and GA were at increased risk. Two studies looked specifically at premature infants. Bremer and colleagues monitored 2449 premature infants with a BW of less than 1251 g enrolled in the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity at age 3 and 12 months, and VanderVeen and colleagues monitored 702 infants with a BW of less than 1251 g enrolled in the multicenter Early Treatment for Retinopathy of Prematurity Trial at age 6 and 9 months. On the basis of multivariate analysis both studies found that BW and GA were not significantly associated with the development of strabismus. These studies were limited because they assessed only severely premature infants who were at a substantially high risk for ROP.

To try to better understand the effect of BW and GA on the risk of developing subsequent strabismus, we used health care claims data from a large, diverse sample of more than 38 000 premature but otherwise healthy children enrolled in a nationwide US managed care network.

Methods

Data Source

The Clinformatics Data Mart database (Optum Inc) contains detailed deidentified records of beneficiaries in a nationwide managed care network including health care claims from January 1, 2001, through December 31, 2011, for 18.5 million enrollees aged 0 to 21 years. For each enrollee, we had access to all medical claims and sociodemographic information including age, sex, race, and family household net worth. A similar database has been used for older individuals. The University of Michigan Institutional Review Board determined that use of these data was exempt from requiring its approval.

Sample Selection

We identified 38 055 children who were born prematurely but were otherwise healthy and were enrolled in the managed care plan continuously since birth for at least 6 months. Prematurity status was identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) billing codes for prematurity (765.1x) or extreme immaturity (765.0x) (eTable 2 in the Supplement). The overall health of each child was quantified using commercial software (Clinical Risk Group [CRG]; 3M Health Information Systems).

The CRG classification system for risk adjustment assigns each individual to 1 of 1080 mutually exclusive risk groups based on his or her historical clinical and demographic characteristics available in claims data. Chronic conditions are defined as physical, mental, emotional, behavioral, or developmental disorders that are expected to last at least 12 months or have sequelae that last at least 12 months and require ongoing treatment and/or monitoring. All CRGs can be folded into 9 CRG statuses. We classified infants based on the information from their first year of life and included those whose CRG status was characterized as healthy” (status 1) or history of significant acute disease (status 2 [eg, upper respiratory tract infection]). Children who were chronically ill (CRG statuses 3-9) were excluded because some of these children may have been too sick for ophthalmologic evaluations or their medical comorbidities may have limited the ability for an eye provider to adequately assess the child for strabismus. Time in the health plan was measured starting at the date of the birth identified by Current Procedural Terminology, Fourth Edition, billing codes V30.xx to V39.xx.

Key Predictors

The 2 key predictors of interest were GA and BW: ICD-9-CM code 765.2x identified the GA of children born prematurely and ranged from less than 24 weeks to 37 weeks. For selected analyses, GA was treated as a continuous variable. For others, it was treated as a binary variable: infants whose GA was 32 weeks or less were defined as very premature and those with a GA of greater than 32 weeks (but <37 weeks) were defined as mildly premature. The ICD-9-CM code 765.0x or 765.1x identified the BW of children who were born prematurely and ranged from less than 500 g to 2500 g or more. For selected analyses, BW was treated as a continuous variable. For others, it was treated as a binary variable: infants whose BW was less than 2000 g were defined as very low BW and those who BW was 2000 g or more were considered mildly low BW. Infants with missing or unspecified GA and BW values were excluded from analyses involving either of these predictor variables.

Primary Outcome

The outcome of interest, diagnosis of strabismus, was captured using ICD-9-CM code 378.xx. To reduce errors in characterizing children with strabismus as a result of miscoding, we required a confirmatory strabismus diagnosis submitted on a separate date. The distribution of the time to initial strabismus diagnosis was estimated by the Kaplan-Meier method.

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Results

A total of 38,055 premature infants met the inclusion criteria (eFigure in the Supplement). The mean time in the plan for eligible children was 2.5 years, ranging from 6 months (inclusion criterion) to 11 years (maximum available data from 2001 to 2011). The sample included 18,234 infant girls (47.9%) among those with known race, there were 25,022 whites (74.3%), 2,831 blacks (8.4%), 3,377 Latinos (10.0%), 1,900 Asians (5.6%), and 567 individuals of other races (1.7%). Most children came from urban households (34,651 [91.9%]), and 13,996 (45.5%) had household net worth of more than $150,000 ($31,831 [10.3%], 7,292 [7%]). Cumulative incidence of amblyopia (ICD-9-CM code 378.4x) in the children in our study was 4.2% at 10 years.

BW and GA

Among 25,601 premature infants with known BW and GA, 6,571 (25.7%) had a very low BW and 19,030 (74.3%) had a mildly low BW. There were 36,45 (14.2%) infants who were very premature and 21,956 (85.8%) who were mildly premature. As expected, among 36,45 infants who were very premature, 293 (81.8%) also had a very low BW; among 19,030 infants with a mildly low BW, 18,365 (96.5%) were mildly premature.

Development of Strabismus

A total of 583 premature infants received a diagnosis of strabismus (Table 2). The cumulative incidence of strabismus estimated using the Kaplan-Meier method was 1.4% by age 2 years and 3.0% by age 5 years. Cumulative incidence curves for the entire sample and for each of the 4 primary exposure groups display the age of onset of strabismus from birth to 5 years (Figure 1).

Association Between Strabismus and BW

Premature infants born with a very low BW had a 47% increased hazard of strabismus compared with those with a mildly low BW (unadjusted HR, 1.47; 95% CI, 1.22-1.76) (Table 3 and Figure 2). When we considered BW and GA in an additive model to estimate their relative effects, very low BW increased the risk of strabismus by 49% (HR, 1.49; 95% CI, 1.16-1.92). After adjusting for sex, race, urban/rural residence, household net worth, delivery method, ROP, and other ocular conditions, premature infants with a very low BW had a 61% increased hazard of developing strabismus (adjusted HR, 1.61; 95% CI, 1.22-2.13). Adjusting for the same covariates in a separate model, every 250 g below a 2,500-g BW was associated with a 13% increased hazard of developing strabismus (adjusted HR, 1.13; 95% CI, 1.04-1.23). For example, an infant with a BW of
Risk of Strabismus Among Premature Infants

Table 2. Descriptive Statistics of Birth Covariates

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Strabismus</th>
<th>No Strabismus</th>
</tr>
</thead>
<tbody>
<tr>
<td>All enrollees</td>
<td>38 055 (100)</td>
<td>583 (1.5)</td>
<td>37 472 (98.5)</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;500</td>
<td>206 (0.6)</td>
<td>7 (1.4)</td>
<td>199 (0.6)</td>
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<tr>
<td>500 to &lt;750</td>
<td>82 (0.2)</td>
<td>0</td>
<td>82 (0.2)</td>
</tr>
<tr>
<td>750 to &lt;1000</td>
<td>104 (0.3)</td>
<td>1 (0.2)</td>
<td>103 (0.3)</td>
</tr>
<tr>
<td>1000 to &lt;1250</td>
<td>647 (1.9)</td>
<td>18 (3.5)</td>
<td>629 (1.9)</td>
</tr>
<tr>
<td>1250 to &lt;1500</td>
<td>1368 (4.0)</td>
<td>22 (4.3)</td>
<td>1346 (4.0)</td>
</tr>
<tr>
<td>1500 to &lt;1750</td>
<td>2336 (6.9)</td>
<td>51 (9.9)</td>
<td>2285 (6.9)</td>
</tr>
<tr>
<td>1750 to &lt;2000</td>
<td>3806 (11.3)</td>
<td>72 (14.0)</td>
<td>3734 (11.2)</td>
</tr>
<tr>
<td>2000 to &lt;2500</td>
<td>11 274 (33.3)</td>
<td>168 (32.6)</td>
<td>11 106 (33.4)</td>
</tr>
<tr>
<td>≥2500</td>
<td>13 991 (41.4)</td>
<td>177 (34.3)</td>
<td>13 814 (41.5)</td>
</tr>
<tr>
<td>Unspecified</td>
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<td>58</td>
<td>3707</td>
</tr>
<tr>
<td>Missing</td>
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<td>9</td>
<td>467</td>
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<tr>
<td>Gestational age, wk</td>
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<tr>
<td>&lt;24</td>
<td>39 (0.1)</td>
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<td>24</td>
<td>14 (0.1)</td>
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<td>25-26</td>
<td>42 (0.2)</td>
<td>0</td>
<td>42 (0.2)</td>
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<td>27-28</td>
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<td>94 (0.4)</td>
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<tr>
<td>29-30</td>
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<td>31-32</td>
<td>2717 (10.2)</td>
<td>56 (14.9)</td>
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<td>35-36</td>
<td>13 314 (50.2)</td>
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<tr>
<td>≥37</td>
<td>2311 (8.7)</td>
<td>31 (8.2)</td>
<td>2280 (8.7)</td>
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<tr>
<td>Missing</td>
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<td>202</td>
<td>11 156</td>
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<tr>
<td>GA, BW</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>GA ≥32 wk, BW &lt;2000 g</td>
<td>2980 (11.6)</td>
<td>68 (18.7)</td>
<td>2912 (11.5)</td>
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<tr>
<td>GA &lt;32 wk, BW ≥2000 g</td>
<td>3591 (14.0)</td>
<td>60 (16.5)</td>
<td>3531 (14.0)</td>
</tr>
<tr>
<td>GA ≥32 wk, BW ≥2000 g</td>
<td>18 365 (71.7)</td>
<td>233 (64.0)</td>
<td>18 132 (71.8)</td>
</tr>
<tr>
<td>GA &lt;32 wk, BW ≥2000 g</td>
<td>665 (2.6)</td>
<td>3 (0.8)</td>
<td>662 (2.6)</td>
</tr>
<tr>
<td>Missing ≥1 variable</td>
<td>12 454</td>
<td>219</td>
<td>12 235</td>
</tr>
</tbody>
</table>

Abbreviations: BW, birth weight; GA, gestational age.

1500 g had a 63% (1.13^4 = 1.63) increased risk relative to a 2500-g premature infant. Thus, the models using continuous and binary forms of the primary predictor exhibited substantively equal conclusions.

Association Between Strabismus and GA
When GA was considered alone, very premature infants were found to have a 48% increased hazard of strabismus relative to mildly premature infants (unadjusted HR, 1.48; 95% CI, 1.15-1.90) (Table 3 and Figure 2). When we considered GA and BW together in an additive model to determine their relative effects, very premature infants did not have a significantly different strabismus risk relative to mildly premature infants (adjusted HR, 1.12; 95% CI, 0.83-1.52). After adjustment for BW and other potential confounders, there was no significant association between strabismus and GA (adjusted HR, 0.98; 95% CI, 0.69-1.38). Adjusting for the same covariates in a separate model, each additional week of prematurity was associated with a statistically nonsignificant 2% decreased hazard of developing strabismus (adjusted HR, 0.98; 95% CI, 0.91-0.95).

Interactions Between BW and GA
The joint exposure model allowed more detailed comparisons of the 4 primary exposure groups (eTable 3 in the Supplement). Compared with the reference group of infants with a mildly low BW and mild prematurity, (1) infants born very prematurely but with a mildly low BW had an 88% reduced risk of strabismus (adjusted HR, 0.12; 95% CI, 0.02-0.87), (2) infants with a very low BW and mild prematurity had a 38% increased risk of strabismus (adjusted HR, 1.38; 95% CI, 1.01-1.88), and (3) infants with a very low BW and born very prematurely had a 75% increased risk of strabismus (adjusted HR, 1.75; 95% CI, 1.27-2.42). There were 2 final comparisons of note: among infants with a very low BW, very premature birth did not confer a statistically significant additional hazard for strabismus (adjusted HR, 1.27; 95% CI, 0.86-1.88), but among infants born very prematurely, a very low BW was associated with a 14-fold increase in the risk of strabismus (adjusted HR, 14.39; 95% CI, 1.99-104.14) relative to those with mildly low BW (Figure 2).

Discussion
In this analysis of 38 055 premature children who were monitored longitudinally for at least 6 months, we found, after accounting for potential confounding factors, that BW appears...
to affect the risk of strabismus much more than GA does. Premature infants who weighed less than 2000 g at birth were found to have a 61% increased hazard of strabismus, independent of GA and other factors. By comparison, with consideration of BW and other variables, premature infants born at 32 weeks or less had no significantly different risk of strabismus relative to infants born after 32 weeks. In the joint exposure model, infants who were born with both putative risk factors (ie, very premature with very low BW) had more than a 14-fold increased risk of strabismus relative to very premature infants with a mildly low BW. Of the 4 groups, infants with the rare (665 of 25,601 [2.6%]) covariate combination of very premature and BW only 33842 had a significantly lower risk of strabismus (<.005) relative to those born at less than 28 weeks and between 28 and 32 weeks.

Data from the Multi-Ethnic Pediatric Eye Disease Study and the Baltimore Pediatric Eye Disease Study also demonstrated that after multivariate analysis, infants with a GA of less than 33 weeks had considerably higher odds (odds ratio, 2.48; 95% CI, 1.17-5.25) for the development of strabismus relative to those with a GA of 33 weeks or more. Unfortunately, neither study considered BW. Because it is known that BW is correlated with GA, it is possible that the findings observed in these analyses may be more attributable to BW than to GA.

Several prior studies have considered the effect of both GA and BW on strabismus without considering BW. One small longitudinal study by Schalij-Delfos et al that followed 99 premature children for 5 years found that those born at greater than 32 weeks’ GA had a significantly lower risk of strabismus (P = .005) relative to those born at less than 28 weeks and between 28 and 32 weeks. Data from the Multi-Ethnic Pediatric Eye Disease Study and the Baltimore Pediatric Eye Disease Study also demonstrated that after multivariate analysis, infants with a GA of less than 33 weeks had considerably higher odds (odds ratio, 2.48; 95% CI, 1.17-5.25) for the development of strabismus relative to those with a GA of 33 weeks or more. Unfortunately, neither study considered BW. Because it is known that BW is correlated with GA, it is possible that the findings observed in these analyses may be more attributable to BW than to GA.

Several prior studies have considered the effect of both GA and BW on strabismus risk. The largest and most recent 33 of these is a retrospective population-based cohort study of 96,842 full-term and premature Danish children born between 1996 and 2003. Analysis of the subset of the 13,200 infants with strabismus within this cohort found an increased risk of esotropia with BW of less than 2000 g (relative risk [RR], 2.20; 95% CI, 1.60-3.05), 2000 to 2499 g (RR, 2.35; 95% CI, 1.80-3.07), and 2500 to 2999 g (RR, 1.29; 95% CI, 1.04-1.58) relative to 3000 to 3499 g (reference group); this relationship was affected very little after adjustment for GA. The increased risk of esotropia found in infants with a GA of 33 to 36 weeks compared with those whose GA was 37 to 41 weeks (reference group) was significantly diminished after adjustment for BW, although it remained statistically significant (RR, 1.39; 95% CI, 1.07-1.81). Although this study did not adjust for possible confounding risk factors as we did, it is notable that in both the Danish study and our present study, BW seemed to be the biggest driver of strabismus risk compared with GA. Direct comparisons of these prior studies with one another and with our study is challenging because of differences in how BW and GA are characterized, variation in the potential confounding risk factors adjusted for in the analyses, the types of providers evaluating the children, and the providers’ experience in diagnosing strabismus. In addition, our study included infants covered by a commercial insurance carrier; infants of lower socioeconomic status were likely underrepresented in our study population.
Nevertheless, previous studies have associated low and very low BW with a negative effect on physical growth, mental development, motor performance, and balance. Therefore, it is not surprising that we found BW to be associated with the development of strabismus, which signals impaired physical or motor development.

Aside from BW and GA, other studies have noted an association between method of delivery and the risk of strabismus. In the present analysis, when we adjusted for BW and GA, we found no statistically significant difference in strabismus risk among children born by vaginal delivery vs cesarean delivery.

The 2012 American Academy of Ophthalmology Preferred Practice Pattern for Pediatric Eye Evaluations offers guidelines on how frequently children should undergo ocular examinations to check for strabismus and other ocular diseases. Neither these guidelines nor guidelines put forth by the American Academy of Pediatrics recommend that clinicians carefully monitor premature infants of low BW for strabismus and amblyopia beyond the standard monitoring in the first 10 weeks of life to check for ROP. Based on the findings of our analysis and the analyses of others, future guidelines may consider recommending that premature infants with low BW undergo periodic assessment in the first few years of life to check for strabismus.

The strengths of this study include the large number of premature children in the sample and the ability to monitor these infants longitudinally over time, even if they changed pediatricians or eye care providers, providing they maintained the same insurance coverage. We captured care provided to prematurely born infants in communities throughout the United States, not just those receiving care at a particular academic medical center or residing in one community setting. Thus, our findings may be more generalizable than findings of some prior analyses. The data regarding BW, GA, and other factors were obtained directly from health care providers, which may be more accurate than parental reports. Finally, we were able to adjust for a variety of potential confounding factors.

Our study has several limitations. As with all analyses that rely on claims data, the data source used here lacks information on several important clinical factors that are known to affect the risk of strabismus. For example, past studies have demonstrated an association between prematurity and myopia even outside the context of ROP. Refractive error (myopia, hyperopia, and astigmatism) and family history of strabismus can predispose patients to different forms of strabismus. With claims data, however, we are unable to capture the type or degree of refractive error in each child or determine whether there was a family history of strabismus. We were therefore unable to account for these factors in our models. Because claims data are used primarily for billing rather than for research purposes, coding errors may exist and we were unable to confirm the accuracy of the strabismus diagnosis, ascertain the severity of disease, or assess the effect of BW and GA on the specific type of strabismus observed. We tried to reduce mischaracterization of children with strabismus resulting from miscoding by requiring 2 or more diagnostic codes for this condition on 2 distinct dates. The providers who were diagnosing strabismus in this analysis varied in their level of experience and training; this may have affected our results, although unless there was differential misdiagnosis of strabismus based on BW or GA, the bias associated with the misclassification would have tended toward reducing the significance and supporting the null hypothesis. Finally, the families of all of these children had health insurance, so our findings may not be generalizable to uninsured or underinsured groups who may be at greater risk for prematurely born infants. Our findings also may not be generalizable to premature infants with chronic health problems because we excluded them from our study.

Conclusions

Based on the findings of this analysis and others, existing guidelines set forth by the American Academy of Pediatrics, American Academy of Ophthalmology, and other organizations should be reassessed for the inclusion of low BW as a key risk factor for developing strabismus. These premature children are at increased risk for irreversible vision loss if their strabismus is not detected and treated early; therefore, they need to undergo periodic evaluation.

REFERENCES


