The Impact of Modest Prematurity on Visual Function at Age 6 Years

Findings From a Population-Based Study

Dana Robaei, MBBS, MPH; Annette Kifley, MBBS, MAppStat; Glen A. Gole, MD, FRANZCO; Paul Mitchell, MD, PhD, FRANZCO

Objective: To determine the effects of modest low birth weight and prematurity on visual function of children predominantly aged 6 years.

Methods: Children with a birth weight of 1500 to 2499 g were considered exposed to a modest low birth weight (n=82) and were compared with children with a birth weight of 2500 g or more (n=1386). Exposure to modest prematurity, 32 to 36 weeks' gestation (n=115), was similarly analyzed and compared with birth at term, 37 or more weeks' gestation (n=1446). Logarithm of the minimum angle of resolution visual acuity was measured in both eyes. Cycloplegic autorefraction (cyclopentolate), cover testing, and dilated fundus examinations were performed.

Results: A modest low birth weight increased the risk of amblyopia (relative risk [RR], 5.1; 95% confidence interval [CI], 2.2-12.0), strabismus (RR, 3.7; 95% CI, 1.5-9.1), and anisometropia (RR, 3.7; 95% CI, 1.2-11.1), together with an increased risk of uncorrected visual acuity in the lowest quartile (RR, 1.7; 95% CI, 1.3-2.2). Modest prematurity increased the risk of amblyopia (RR, 4.5; 95% CI, 1.9-10.6), strabismus (RR, 2.6; 95% CI, 1.1-6.0), and uncorrected visual acuity in the lowest quartile (RR, 1.5; 95% CI, 1.1-2.0).

Conclusion: Modest degrees of low birth weight and prematurity may be associated with increased ophthalmic morbidity at age 6 years.

Arch Ophthalmol. 2006;124:871-877

THE WORLD HEALTH ORGANIZATION defines low birth weight as less than 2500 g and prematurity as birth before 37 weeks' gestation. Retinopathy of prematurity (ROP) is known to be associated with subsequent ophthalmic impairment in children of very low birth weight (<1500 g) or very early gestational age (<32 weeks). These children are also at risk of visual pathway damage by intraventricular hemorrhage, periventricular leukomalacia, and other lesions. Increased ocular morbidity in very premature infants has been extensively documented and these factors have been variably implicated. With the exception of the important contributions of Fledelius on ocular biometry and refraction in children born with a birth weight of less than 2000 g, scant literature exists on the prevalence of ocular morbidity in children with a birth weight of 1500 to less than 2500 g or in those born between 32 and 36 weeks' gestation.

Very preterm neonates constituted only 1.6% of infants born in Australia from 1997 to 2001, while those born at 32 to 36 weeks' gestation constituted 6.0% of all births during this period. Most previous studies of the latter were not population based and often did not compare findings with children born at term. Furthermore, there is no uniform agreement regarding the importance, for subsequent ocular development, of prematurity compared with low birth weight, a marker of intrauterine growth retardation. In determining exposure to low birth weight or prematurity, studies have used a birth weight cutoff, a gestational age cutoff, or a combination, resulting in a heterogeneous case mix, with study findings that cannot be easily compared.

We aimed to determine whether either modest low birth weight (1500-2500 g) or modest prematurity (gestational age, 32-36 weeks) affects ocular morbidity at the age of 6 years.
METHODS

POPULATION STUDIED

The Sydney Myopia Study is a population-based survey of refraction and eye disease in 6-year-old schoolchildren residing in metropolitan Sydney, Australia. It forms part of the Sydney Childhood Eye Study, which is examining childhood eye conditions across a range of ages. Methods used to select the target sample and study procedures are reported. In brief, the study area was stratified by socioeconomic status, using Australian 2001 national census data, to select 34 primary schools across Sydney. This report includes data from year 1 schoolchildren examined from August 2003 to October 2004.

PROCEDURES

Written consent from at least one parent, plus assent of each child, was obtained. The study was approved by the University of Sydney Human Research Ethics Committee and the Department of Education, New South Wales.

Visual acuity was tested binocularly using a logarithm of minimum angle of resolution (logMAR) chart (Tori-vision CSV-1000; Vectorvision Inc, Dayton, Ohio), read at 244 cm (8 ft). Visual acuity was assessed with and without spectacle correction, if worn, and with a 1.2-mm pinhole aperture for reduced visual acuity (≤20/32) or greater than 1-line (5-letter) difference between eyes. A cylinder of 0.75 diopter (D) or more was corrected by subjective refraction. For each eye, visual acuity was recorded as the number of letters read correctly from 0 (<20/200) to 70 (20/10).

Cycloplegia was induced using 2 cycles of 1% cyclopentolate and 1% tropicamide, instilled 5 minutes apart, after corneal anesthesia with 1% amethocaine, and followed by cycloplegic autorefraction (Canon RK-F1; Canon Inc, Kanagawa, Japan). Children also had a comprehensive eye examination, including a cover test, a prism bar cover test, assessment of ocular movements, stereoscopic vision testing, ocular biometry, a slitlamp examination, and retinal photography.

Parents completed a comprehensive 193-item questionnaire that included the child's birth and medical history, maternal obstetric history, and sociodemographic information covering parental age, ethnicity, country of birth, education, and occupation. All Australian children are given a health record booklet at birth; health professionals accurately enter the child's variables in this booklet at birth, namely, birth weight, birth length, head circumference, gestational age, and mode of delivery. We asked parents to extract this information from their child's health record booklet.

DEFINITIONS

The following findings are based on a nonconcurrent cohort study nested within the larger survey. Exposure was determined retrospectively, and prevalence of ocular morbidity was assessed at the age of 6 years. Modest low birth weight (1500-2499 g) was defined as the exposure. Exposed children were compared with children with a normal birth weight (≥2500 g) for various sociodemographic and perinatal characteristics and ocular outcomes at the age of 6 years. Modest prematurity (gestational age, 32-36 weeks) was similarly defined as the exposure and these children were compared with children born at term (gestational age, ≥37 weeks). Myopia was defined as spherical equivalent (SE) refraction of −0.50 D or less, and hyperopia as SE refraction of 2.0 D or more, deemed significant if 3.0 D or more. Astigmatism was defined as a cylinder of 1.0 D or more, and anisometropia as a between-eye SE refraction difference of 1.0 D or more. "Normal" refraction was defined as SE refraction of greater than −0.50 D to less than 2.0 D.

Strabismus was defined as any strabismus on cover testing at near or distance fixation. Amblyopia was defined as a corrected visual acuity of less than 0.3 logMAR unit (<40 letters, Snellen equivalent, <20/40) in the affected eye, not attributable to an ocular or visual pathway structural abnormality, plus a 2-logMAR line difference between the 2 eyes, in the presence of an amblyogenic factor such as anisometropia, strabismus, high ametropia, or form deprivation. Stereoscopic vision was screened using the Lang II test (Lang-stereotest; Forsch Switzerland); children were assigned full binocular stereoscopic vision if they could recognize all 4 shapes.

Visual impairment was defined in better and worse eyes using 0.3 logMAR unit as the uncorrected visual acuity cutoff. Detailed findings on visual impairment and refraction for the sample are reported elsewhere.

The child's ethnic origin was derived from both parents. Children whose parents were of different ethnicities were considered to have a mixed ethnicity. Parental education was defined as the highest education level completed by either parent. Socioeconomic status was based on parent's home ownership and employment status.

DATA HANDLING AND STATISTICAL ANALYSIS

Data were entered into a computer program (Microsoft Access). Statistical analyses were performed using SAS statistical software (Version 8.2; SAS Institute Inc, Cary, NC). Mixed models and generalized estimating equations adjusted for clustering within schools; where not significant, χ2 and t tests were used. In light of the number of statistical tests involved in a study such as this, the possibility of some chance findings should be borne in mind, although these tests were all targeted toward a priori questions. Provision of sample means and mean differences with their standard errors, as well as relative risks (RRs) with their 95% confidence intervals (CIs), allows the reader to assess the strength of each finding.

RESULTS

ALL SUBJECTS

Of the 2238 eligible children, 1765 (78.9%) were given parental permission to participate and 1740 (77.8%) were available at examination. The mean age of the 1740 participants was 6.7 years (range, 5.5-8.4 years), and 49.4% were female. Most (70.4%) were aged 6 years, while 25.5% were aged 7 years. Data on birth weight and/or gestational age were available for 1593 children.

ANALYSIS BY BIRTH WEIGHT AND GESTATIONAL AGE SEPARATELY

Parents provided birth weight data for 1479 children (85.0% of the participants). The mean birth weight for the entire sample was 3374 g (95% CI, 3329-3420 g); 82 children (5.5%) with a modest low birth weight (1500-2499 g) were assigned as exposed and compared with 1386 children (93.7%) with a normal birth weight (≥2500 g).

Parents provided gestational age data for 1574 children (90.5% of the participants). 115 children (7.3%) were modestly premature (gestational age, 32-36 weeks) and...
were considered exposed and compared with 1446 children (91.9%) born at term (gestational age, ≥37 weeks). This left 13 children with a very low birth weight (<1500 g) or a very early gestational age (<32 weeks) who were excluded from initial analyses.

**SOCIODEMOGRAPHIC AND PERINATAL CHARACTERISTICS**

Table 1 outlines selected sociodemographic and perinatal characteristics for children exposed to a modest low birth weight and children with a normal birth weight. Exposed children were slightly older at examination. The 2 groups were comparable for sex, ethnicity, and socioeconomic status. Compared with mothers of nonexposed children, mothers of modestly low-birth-weight children were older and more likely to have smoked or been ill during the pregnancy. Children with a modest low birth weight were more likely to have been a firstborn child or to have been born by cesarean section.

The pattern of sociodemographic and perinatal differences between exposed and nonexposed children was similar when exposure was defined by gestational age (Table 2) instead of birth weight, except that maternal smoking in pregnancy was not significantly associated with modest prematurity.

---

**VISUAL ACUITY**

The mean uncorrected visual acuity in the worse eye was 47.3 logMAR letters (range, 20-65 logMAR letters) for children exposed to a modest low birth weight and 48.7 logMAR letters (range, 0-60 logMAR letters) for nonexposed children (P=.048). The mean uncorrected visual acuity in the better eye was 49.8 logMAR letters (range, 28-65 logMAR letters) for exposed children and 50.6 logMAR letters (range, 12-63 logMAR letters) for nonexposed children (P=.10). Exposed children were significantly more likely to be in the lowest quartile of uncorrected visual acuity than nonexposed children, for better (RR, 1.7; 95% CI, 1.2-2.4) and worse (RR, 1.7; 95% CI, 1.3-2.2) eyes. The mean corrected visual acuity in better and worse eyes, however, was not significantly different for the 2 groups, although the worse eyes of exposed children were more likely to be in the lowest quartile of corrected visual acuity (RR, 1.4; 95% CI, 1.1-1.9).

The mean visual acuity (uncorrected and corrected) in either the worse or better eyes was not significantly different for children exposed and not exposed to modest prematurity. Exposed children, however, were more likely to be in the lowest quartile of uncorrected visual acuity than nonexposed children, for better (RR, 1.6; 95% CI, 1.1-2.2) and worse (RR, 1.5; 95% CI, 1.1-2.0) eyes.

---

*Data are given as number (percentage) of each group unless otherwise indicated.

†For continuous factors, t test from a mixed linear regression model; and for categorical factors, χ² test from a generalized estimating equation model.

‡Percentages may not total 100 because of rounding.

§Hypertension, diabetes mellitus, high fever, rubella, and mumps.
REFRACTION

The mean SE refraction in right eyes was similar for children exposed and not exposed to a modest low birth weight (1.33 and 1.28 D, respectively; \( P = .58 \)), as was the mean cylinder power. Exposure was not associated with increased risk of myopia, significant hyperopia, or a change in the distribution of the astigmatic axis. Defining exposure as modest prematurity yielded similar findings. A modest low birth weight marginally increased the risk of astigmatism: 8.5% of exposed children had cylinder powers of 1.00 D or more in their right eyes, compared with 3.9% of nonexposed children (RR, 2.2; 95% CI, 1.0-4.9). A similar nonsignificant trend was found for modest prematurity: 6.8% of exposed children had cylinder powers of 1.00 D or more, compared with 4.3% of nonexposed children (\( P = .25 \)).

OCULAR PATHOLOGICAL FEATURES

Table 3 shows the risk of selected ocular outcomes in association with modest low birth weight. Amblyopia was more frequent among exposed than nonexposed children (\( P < .001 \)). Strabismus was also significantly more common among the exposed than the nonexposed children (\( P = .03 \)). Modest prematurity, thus, increased the risk of amblyopia and strabismus by 3- to 5-fold on univariate analysis. A predictably lower proportion of modestly premature children (82.3%) demonstrated full binocular stereoscopic vision than children born at term (92.9%) (\( P = .008 \)). After adjustment for age and significant perinatal factors, modest prematurity still conferred a significantly increased risk of amblyopia (RR, 3.6; 95% CI, 1.6-8.0), but not strabismus (RR, 2.1; 95% CI, 0.8-5.4).

Table 4 shows the RR of selected ocular outcomes in association with modest prematurity. Amblyopia was more frequent among exposed than nonexposed children (\( P < .001 \)). Strabismus was also significantly more common among the exposed than the nonexposed children (\( P = .03 \)). Modest prematurity, thus, increased the risk of amblyopia and strabismus by 3- to 5-fold on univariate analysis. A predictably lower proportion of modestly premature children (82.3%) demonstrated full binocular stereoscopic vision than children born at term (92.9%) (\( P = .008 \)). After adjustment for age and significant perinatal factors, modest prematurity still conferred a significantly increased risk of amblyopia (RR, 3.6; 95% CI, 1.6-8.0), but not strabismus (RR, 2.1; 95% CI, 0.8-5.4).

OCULAR FINDINGS FOR CHILDREN WITH A VERY LOW BIRTH WEIGHT AND/OR A VERY EARLY GESTATIONAL AGE

Our sample included 13 children with a very low birth weight (<1500 g) and/or a very early gestational age (<32 weeks) who were excluded from previous analyses. The prevalence of myopia was significantly higher in this group (15.0%) than in children with a normal birth weight and gestational age (1.4%) (\( P = .01 \)). These children were also significantly more likely to have amblyopia (\( P < .001 \)), strabismus (\( P = .046 \)), and astigmatism (7.7%) and strabismus (8.3%) were consistently, but nonsignificantly, higher in children with a very low birth weight and/or a very early gestational age. The addition of these 13 children to the larger group exposed to modest prematurity or low birth weight did not alter the profile of ocular outcomes described previously.

COMBINED ANALYSIS BY BIRTH WEIGHT AND GESTATIONAL AGE

Of the 92 children with a modest low birth weight, 51 (55.4%) were also born modestly premature. Given the overlap between birth weight and gestational age, we...
Table 5. A Comparison of Ocular Outcomes by a Combination of BW and GA

<table>
<thead>
<tr>
<th>Ocular Outcome</th>
<th>Group A (Nonexposed Children)</th>
<th>Group B (GA ≥37 wk and Normal BW)</th>
<th>Group C (GA ≥37 wk and Low BW)</th>
<th>Group D (GA ≥36 wk and Low BW)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 1304)*</td>
<td>(n = 64)*</td>
<td>(n = 39)*</td>
<td>(n = 51)*</td>
</tr>
<tr>
<td>Visual acuity in the lowest quartile (worse eye)</td>
<td>302 (23.2)</td>
<td>16 (25.0)</td>
<td>14 (35.9)</td>
<td>19 (37.3)</td>
</tr>
<tr>
<td>Uncorrected</td>
<td></td>
<td>.46</td>
<td>.06</td>
<td>.001</td>
</tr>
<tr>
<td>Corrected</td>
<td>252 (19.3)</td>
<td>15 (23.4)</td>
<td>10 (25.6)</td>
<td>14 (27.5)</td>
</tr>
<tr>
<td>Myopia</td>
<td>18 (1.4)</td>
<td>1 (1.6)</td>
<td>0</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Hyperopia (&gt;3.00 D)</td>
<td>35 (2.7)</td>
<td>3 (4.7)</td>
<td>1 (2.6)</td>
<td>3 (5.9)</td>
</tr>
<tr>
<td>Astigmatism</td>
<td>47 (3.6)</td>
<td>4 (6.2)</td>
<td>3 (7.7)</td>
<td>4 (7.8)</td>
</tr>
<tr>
<td>Astigmatism</td>
<td>17 (1.3)</td>
<td>1 (1.6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anisometropia</td>
<td>29 (2.2)</td>
<td>2 (3.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Strabismus</td>
<td>5 (0.4)</td>
<td>2 (3.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Amblyopia</td>
<td>47 (3.6)</td>
<td>4 (6.2)</td>
<td>3 (7.7)</td>
<td>4 (7.8)</td>
</tr>
<tr>
<td>Full BSV</td>
<td>1200 (92.0)</td>
<td>57 (91.1)</td>
<td>52</td>
<td>42</td>
</tr>
</tbody>
</table>

Abbreviations: BSV, binocular stereoscopic vision; BW, birth weight; D, diopters; GA, gestational age; NA, data not applicable.

*Data are given as number (percentage) of each group.
†χ² Test from a generalized estimating equation model.

The risk of amblyopia, strabismus, and anisometropia attributable to modest low birth weight and/or early gestational age was calculated for children exposed (attributable risk among exposed) and for the whole population (population attributable risk). Among children with a low birth weight and/or an early gestational age, either factor may have accounted for around 75% of amblyopia cases. A modest low birth weight and/or an early gestational age may have accounted for 23% of amblyopia cases seen in this population. Corresponding attributable risks for strabismus and anisometropia among exposed children were 63% and 61%, respectively, while population attributable risks for these 2 conditions were 15% and 14%, respectively. These findings were unchanged after controlling for demographic factors (age, sex, and ethnicity) or perinatal factors, reported in Table 1 and Table 2.

This study documents the sociodemographic, perinatal, and ocular characteristics of Australian children exposed to modest prematurity and low birth weight, compared with children born at term or with a normal birth weight. Birth weights and gestational age data were mostly derived from children’s birth record books. The resulting perinatal data for this sample closely agree with values recently published for the Australian population. The mean birth weight for our sample was 3374 g, close to the national mean of 3378 g for children born in Australia from 1997 to 2001. The prevalence of low birth weight, defined as less than 2500 g, in our sample (6.2%) was almost identical to the national figure of 6.1% for the same period. Data on gestational age were also similar to the national mean: 8.0% of our sample was born at less than 37 weeks’ gestation, and the corresponding national figure was 7.6% for 1997 to 2001. This comparison with published national data provides confidence about the representative nature of our study sample.

Neither modest low birth weight nor modest prematurity was significantly related to refraction or myopia prevalence in our sample. This finding is seemingly at odds with many previous studies indicating higher myopia prevalence in premature and/or low-birthweight children, compared with children born at term. These studies, however, differed from ours in 2 important respects. First, some included a proportion of children with a known history of ROP. Second, stud-
ies that excluded children with an ROP history included samples of very premature children. Indeed, the myopia prevalence in our small subsample of very low-birth-weight and/or very premature children was significantly higher than in controls. No myopia relationship was reported by Saw and Chew, whose Singapore sample also included few very premature children, with none having an ROP history.

An increased prevalence of amblyopia in very premature (gestational age, ≤32 weeks) and/or very low-birth-weight (<1500 g) children was previously reported. Our study demonstrates this also in children with a modest low birth weight or prematurity, even after adjustment for other perinatal factors. These 2 factors accounted for 23% of the amblyopia cases seen in our population sample. Strabismus and anisometropia, also known to be associated with extreme prematurity and very low birth weight, were also more prevalent among modestly premature children, although the effect was somewhat diminished after adjustment for other factors, such as maternal illness or smoking during pregnancy.

Although the pathogenesis of amblyopia, strabismus, and anisometropia in the context of prematurity has not been elucidated, the visual history in preterm infants is quite different from that in full-term infants. The development of amblyopia and strabismus in preterm infants may be secondary to subtle cortical effects of perinatal hypoxic-ischemic injury. An increased prevalence of neurological “soft signs” (nonlocalized deficits in motor, sensory, and integrative functions) has been demonstrated in children with a modest low birth weight (1500-2500 g) compared with children with a normal birth weight (>2500 g). Furthermore, these signs have been associated with the presence of intelligence deficits, hyperactivity, and learning disorders, also reportedly more common among children with a modest low birth weight. We showed that mothers of low-birth-weight children were more likely to have smoked or been ill during pregnancy than mothers of normal-birth-weight children. The same adverse conditions that led to their low birth weight could have caused the cerebral and ocular changes that led to amblyopia and strabismus.

Finally, analysis of visual function by either gestational age or birth weight yielded fairly similar results. A modest low birth weight was associated with a similar range of ocular disorders as modest prematurity when compared with a normal birth weight and term birth. We therefore conclude that both variables are equally valid markers of prematurity in relation to subsequent ocular morbidity.

The main strengths of this study are its population-based design, standardized examination protocol, and uniform ascertainment of associated characteristics. This data set varies considerably from clinic-based samples; demonstrated associations are much less likely to be spurious, with findings reasonably generalizable to the childhood population.

A limitation is that the data on maternal smoking and illness during pregnancy were collected retrospectively. Dependence on maternal recall can potentially introduce recall bias, together with reluctance by some women to report smoking during pregnancy. Given that parents were masked to the study hypothesis, this is not likely to have affected our findings. Second, data on history of ROP were not specifically sought. This is also unlikely to have biased the findings, because most of our sample was only modestly premature and the inclusion of very premature children did not significantly alter the findings. A third limitation is the lack of data on other possible explanatory factors, such as maternal diet during pregnancy. Unfortunately, reliable retrospective collection of this information is not likely to be possible.

Previous researchers have considered modest prematurity (gestational age, 32-36 weeks) to be of little clinical importance to subsequent ocular development. While inconclusive, this study shows that prematurity represents a continuum of risk and that even limited degrees may be associated with increased prevalence of amblyopia, strabismus, and anisometropia. This finding has potentially important implications for the follow-up of premature children and, as such, requires confirmation in other population-based studies. Recommendations for ophthalmic follow-up in the United Kingdom are limited to infants considered at risk for severe ROP (ie, those with a birth weight of ≤1500 g and/or a gestational age of ≤31 weeks). The American Academy of Pediatrics similarly recommends follow-up for infants with a birth weight of less than 1500 g or a gestational age of 28 weeks or less.

Based on our findings, even modestly premature children have a greater need for ophthalmic surveillance than their full-term counterparts, and follow-up programs of premature children may need to encompass this wider subgroup. Targeting this specific group of children might also increase the yield of vision screening programs designed to detect amblyopia and strabismus.

Submitted for Publication: September 10, 2005; final revision received December 15, 2005; accepted December 19, 2005.

Correspondence: Paul Mitchell, MD, PhD, FRANZCO, Department of Ophthalmology, Center for Vision Research, University of Sydney, Westmead Hospital, Hawkesbury Road, Westmead, New South Wales 2145, Australia (paul_mitchell@wmi.usyd.edu.au).

Financial Disclosure: None.

REFERENCES
