Risk Factors for Amblyopia in the Vision in Preschoolers Study

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Objective: To evaluate risk factors for unilateral amblyopia and for bilateral amblyopia in the Vision in Preschoolers (VIP) study.

Design: Multicenter, cross-sectional study.

Participants: Three- to 5-year-old Head Start preschoolers from 5 clinical centers, overrepresenting children with vision disorders.

Methods: All children underwent comprehensive eye examinations, including threshold visual acuity (VA), cover testing, and cycloplegic retinoscopy, performed by VIP-certified optometrists and ophthalmologists who were experienced in providing care to children. Monocular threshold VA was tested using a single-surround HOTV letter protocol without correction, and retested with full cycloplegic correction when retest criteria were met. Unilateral amblyopia was defined as an interocular difference in best-corrected VA of 2 lines or more. Bilateral amblyopia was defined as best-corrected VA in each eye worse than 20/50 for 3-year-olds and worse than 20/40 for 4- to 5-year-olds.

Main Outcome Measures: Risk of amblyopia was summarized by the odds ratios and their 95% confidence intervals estimated from logistic regression models.

Results: In this enriched sample of Head Start children (n = 3869), 296 children (7.7%) had unilateral amblyopia, and 144 children (3.7%) had bilateral amblyopia. Presence of strabismus ($P < 0.0001$) and greater magnitude of significant refractive errors (myopia, hyperopia, astigmatism, and anisometropia; $P < 0.00001$ for each) were associated independently with an increased risk of unilateral amblyopia. Presence of strabismus, hyperopia of 2.0 diopters (D) or more, astigmatism of 1.0 D or more, or anisometropia of 0.5 D or more were present in 91% of children with unilateral amblyopia. Greater magnitude of astigmatism ($P < 0.0001$) and bilateral hyperopia ($P < 0.0001$) were associated independently with increased risk of bilateral amblyopia. Bilateral hyperopia of 3.0 D or more or astigmatism of 1.0 D or more were present in 76% of children with bilateral amblyopia.

Conclusions: Strabismus and significant refractive errors were risk factors for unilateral amblyopia. Bilateral astigmatism and bilateral hyperopia were risk factors for bilateral amblyopia. Despite differences in selection of the study population, these results validated the findings from the Multi-Ethnic Pediatric Eye Disease Study and Baltimore Pediatric Eye Disease Study. *Ophthalmology 2014;121:622-629 © 2014 by the American Academy of Ophthalmology.*

**Supplemental material is available at www.aaojournal.org.*

See editorial on page 617.

Vision disorders are the fourth most prevalent disability among children in the United States, with amblyopia being the leading cause of vision impairment among children.[1,2] Amblyopia, also referred to as lazy eye in colloquial terms, is a childhood vision disorder affecting 1% to 4% of preschool-aged children.[3–7] Amblyopia usually occurs unilaterally but also can be present bilaterally. Studies have shown that if amblyopia is left undetected or untreated, children are at high risk of developing further vision impairment into adulthood as a result of damage to the better-seeing eye or development of a disease such as macular degeneration.[8,9] Historically, there has been good agreement among eye care practitioners that detecting and treating amblyopia in early childhood is desirable to prevent permanent loss of vision. Early detection is critical in increasing the likelihood of effective treatment.[10,11] Treatment of amblyopia at a young age is highly successful.[12,13] As a result, identification of risk factors for amblyopia is of great importance to assist eye care practitioners in their screening for identifying high-risk children who may benefit from earlier interventions for improved vision outcome.

Strabismus and refractive error are 2 well-known risk factors of amblyopia in children.[2] However, the exact magnitude of associations with amblyopia for each type of strabismus (esotropia and exotropia) and with various degrees of each refractive error (myopia, hyperopia, astigmatism, and anisometropia) has not been evaluated fully because of the limited number of amblyopia cases in most studies. A recent pooled report from the 2 largest United States population-based samples of preschool

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children of the Multi-Ethnic Pediatric Eye Disease Study (MEPEDS) and Baltimore Pediatric Eye Disease (BPEDS) estimated the risk of amblyopia for each type of strabismus and severity level of refractive error. The study found that only esotropia (not exotropia) was associated with unilateral amblyopia, and the threshold level of refractive error associated with increased risk of amblyopia was lower than previously reported.[14]

The Vision in Preschoolers (VIP) study is a multicenter study that oversampled children with vision disorders and had a large sample of children with unilateral amblyopia (n = 296) or bilateral amblyopia (n = 144). The VIP study data provided an excellent opportunity to validate the associations of strabismus and refractive error with amblyopia found in previous studies.[6,14] The goal of this report was to evaluate the association of amblyopia with type of strabismus and with severity level of refractive error (myopia, hyperopia, astigmatism, and anisometropia). By identifying the thresholds of refractive error associated with increased risk of amblyopia, referral criteria for vision screening can be optimized to improve identification of high-risk children for further evaluation or treatment.

Methods

This is a secondary analysis of data from the VIP Study. The VIP study is a multicenter cross-sectional study that evaluated the effectiveness of various vision screening tests to detect vision disorders in preschool children. A total of 4040 VIP participants (36–72 months of age) were enrolled from Head Start programs near the 5 VIP clinical centers across the United States: Berkeley, California; Boston, Massachusetts; Columbus, Ohio; Philadelphia, Pennsylvania; and Tahlequah, Oklahoma). All Head Start children who failed and a random sample of those who did not fail their local Head Start screening were targeted for enrollment into the VIP study. This approach provided a study population in which children with ocular disorders were overrepresented. The local institutional review boards associated with each center approved the study protocol, and informed consent documents were obtained from children's parents or guardians.

Details of the VIP study have been published previously.[1,15] Only the details of the comprehensive eye examinations for determining amblyopia, strabismus, and refractive error related to this article are described here.

Comprehensive Eye Examinations

The enrolled children underwent a comprehensive eye examination performed by study-certified ophthalmologists and optometrists who were experienced in providing care to children. The comprehensive eye examination included monocular threshold visual acuity (VA) testing, cover testing, and cycloplegic retinoscopy. Examination results were used to determine whether a child had amblyopia, strabismus, significant refractive error, or a combination thereof. Anterior segment evaluation and dilated fundus examination also were performed to detect other possible causes of reduced VA.

Monocular threshold VA testing was conducted with crowded, single H, O, T, and V optotypes using the Electronic Vision Assessment system at 10 feet, according to the protocol for the Amblyopia Treatment Studies.[16] Children who wore spectacles were tested while wearing their spectacles. Both eyes of a child were retested on the same day with full cycloplegic correction if (1) VA was worse than 20/50 for 3-year-olds, VA was worse than 20/40 for 4- to 5-year-olds, or there was an interocular acuity difference (IAD) of 2 lines or more; and (2) hyperopia of 2.0 diopters (D) or more, or myopia of 0.5 D or more, or astigmatism of 1.0 D or more was present in either eye. Seven hundred twenty children (18%) in the VIP study met the retest criteria and were retested. The final VA score of an eye was based on the best VA score achieved from either initial test or retest.

Both a cover–uncover test and an alternating cover test were performed at distance (10 feet) and near (16 inches) to evaluate ocular alignment. Cycloplegic retinoscopy was performed to measure the refractive error. Retinoscopy was performed 30 to 40 minutes after instillation of 1 drop of 0.5% proparacaine, followed by 1 drop each of 1% cyclopentolate and 0.5% tropicamide. A second set of the cycloplegic agents was instilled at the examiner's discretion. Retinoscopy was performed with the child wearing retinoscopy spectacles corresponding to the screener's working distance to control any residual accommodation. The child was instructed to fixate on an animated video target presented at 3 m. The examiner used a lens rack or handheld trial lenses to neutralize the refractive error in each eye. Measurements were obtained along the 2 principal meridia of each eye.

Amblyopia Determination

Unilateral amblyopia was defined as 2 lines or more of difference in best-corrected interocular VA, without considering the presence or absence of amblyopia risk factors. Because the VIP study protocol did not require retesting a child with best correction when the IAD was fewer than 2 lines and VA in each eye was in the normal range for the child's age, these children were classified as nonamblyopic under the assumption that the IAD would remain at fewer than 2 lines on retesting. Children with IAD of 2 lines or more who were not retested with correction (because their small amount of refractive error did not meet retest criteria as defined above; n = 160) were excluded from analysis because it is unknown whether retesting with correction would have resulted in a smaller IAD.

Bilateral amblyopia was defined as best-corrected VA in each eye worse than 20/50 for 3-year-olds and worse than 20/40 for the 4- to 5-year-olds. Under the definitions of unilateral amblyopia and bilateral amblyopia, a child could have both unilateral amblyopia and bilateral amblyopia. If a child met the definition of both unilateral amblyopia and bilateral amblyopia, the child was classified as having unilateral amblyopia in the analysis for risk factors of unilateral amblyopia and was classified as having bilateral amblyopia in the analysis for risk factors of bilateral amblyopia.

Risk Factors

In the VIP study, demographic information (birth date, sex, race, and ethnicity) of a child was collected at enrollment based on information provided by the child's parent or legal guardian. For easier comparison with other studies race or ethnicity was classified as American Indian, Asian, black, non-Hispanic white, Hispanic, and other/unknown (for those reported with more than 1 race category or those without race information). Age was calculated as the difference between date of comprehensive eye examination and birth date and was grouped as 36 to 47, 48 to 59, or 60 to 72 months.

Ocular risk factors were defined based on findings from comprehensive eye examinations. Strabismus status was classified as esotropia, exotropia, or no horizontal strabismus. To facilitate comparison of our findings with those from other studies, we

defined the presence and severity level of the ocular risk factors similarly to those of other studies.[6,14] For the ocular risk factor of unilateral amblyopia, we determined each type of refractive error based on the worse eye because we assumed that the ocular condition in the worse eye dominated the association with unilateral amblyopia. We classified the presence and severity levels for myopia (<0.5 D, ≥0.5−<2 D, and ≥2 D), hyperopia (<2 D, ≥2−<3 D, ≥3−<4 D, ≥4−<5 D, ≥5−<6 D, and ≥6 D), astigmatism (<1 D, ≥1−<2 D, ≥2−<3 D, ≥3−<4 D, and ≥4 D), and spherical equivalent anisometropia (<0.5 D, ≥0.5−<1, ≥1−<2 D, and ≥2 D). For the ocular risk factors of bilateral amblyopia, we defined bilateral astigmatism and bilateral hyperopia based on the results of the better eye. Because bilateral amblyopia is a condition affecting both eyes, we required that both eyes should have the refractive error to qualify it as an ocular risk factor for bilateral amblyopia.

Statistical Analysis

The risk factors for unilateral amblyopia and for bilateral amblyopia were first evaluated using univariate analysis through logistic regression models. Risk factors with $P < 0.10$ from univariate analysis were included in the multivariate logistic regression models. The multivariate logistic regression models were developed with the backward model selection by dropping out nonsignificant risk factors one at a time, and the final model kept only statistically significant ($P < 0.05$) risk factors. The odds ratio (OR) and its 95% confidence interval for each of the significant risk factors were calculated from the final multivariate logistic regression model.

To explore further how refractive errors at various levels were associated with unilateral amblyopia and with bilateral amblyopia, detailed descriptive analyses were performed by calculating the proportion of amblyopia at various levels of refractive error at 0.25-D increments, and the proportion with amblyopia at different levels of refractive error then was fitted by the locally weighted scatterplot smoothing curve. After the significant risk factors for unilateral amblyopia and bilateral amblyopia were determined, the composition of significant risk factors was examined (at the threshold level associated with increased risk of amblyopia) among children with unilateral amblyopia and among children with bilateral amblyopia.

All statistical analyses were performed using SAS software version 9.2 (SAS Inc., Cary, NC). Two-sided P values less than 0.05 were considered to be statistically significant and no adjustment for multiple comparisons was applied.

Results

Study Subjects

A total of 4040 preschoolers were enrolled into VIP phases 1 and 2; 160 children (4.0%) were excluded because of having an interocular difference of 2 lines or more but were not retested because their refractive error did not meet retest criteria. An additional 11 children (0.2%) were excluded because of missing refractive error measurements. As a result, the remaining 3869 subjects were analyzed for this study.

Among 3869 preschoolers, 794 (20.5%) were 3-year-olds, 2068 (53.9%) were 4-year-olds, and 1007 (26.0%) were 5-year-olds. Sex was distributed equally. Approximately half (51%) were black; the remaining were Hispanic (20%), non-Hispanic white (11.8%), American Indian (8.5%), Asian (3.7%), and other (4.6%). Based on the findings from comprehensive eye examinations of 3869 preschoolers, overrepresenting children with ocular conditions, 91 (2.4%) had esotropia, 49 (1.3%) had exotropia, 440 (11.3%) had myopia of 0.5 D or more, 1533 (39.6%) had hyperopia of 2.0 D or more, 1118 (28.9%) had astigmatism of 1.0 D or more in either eye, and 927 (24.0%) had any anisometropia of 0.5 D or more. A total of 734 children (19.0%) had astigmatism of 1.0 D or more in both eyes, and 1159 (30.0%) had bilateral hyperopia of 2.0 D or more; 296 children (7.7%) had unilateral amblyopia and 144 children (3.7%) had bilateral amblyopia. Twenty-three children (0.6%) had both unilateral and bilateral amblyopia.

Risk Factors for Unilateral Amblyopia

The results from univariate analysis for demographic and ocular risk factors for unilateral amblyopia are shown in Table 1 (available at www.aaojournal.org). In children 36 to 72 months of age, age was not associated with unilateral amblyopia ($P = 0.69$). Overall, race or ethnicity was not associated with unilateral amblyopia ($P = 0.19$); however, the proportion of children with unilateral amblyopia was higher among Hispanic children than non-Hispanic children (9.4% vs. 7.2%; $P = 0.03$). Refractive error (myopia, hyperopia, astigmatism, anisometropia) and strabismus were associated significantly with unilateral amblyopia (all $P < 0.0001$). Further descriptive analyses of the association between different levels of refractive error and unilateral amblyopia showed that the proportion of unilateral amblyopia increased as the magnitude of each type of refractive error increased (Table 2, available at www.aaojournal.org; Fig 1).

Table 3 provides multivariate analysis results for significant risk factors for unilateral amblyopia. Myopia was associated with unilateral amblyopia ($P < 0.0001$). Compared with nonmyopic children (<0.5 D), the OR was 1.7 for myopia of 0.5 to 2.0 D and 4.1 for myopia of 2.0 D or worse. Hyperopia was associated with unilateral amblyopia ($P < 0.0001$) in a dose-dependent manner, with an OR of 1.8 for hyperopia of 2 to 3 D, 2.5 for hyperopia of between 3 to 4 D, 4.6 for hyperopia of 4 to 5 D, and 4.3 for hyperopia of 5.0 D or more. Astigmatism was associated significantly with unilateral amblyopia ($P < 0.0001$), with an OR of 2.2 for astigmatism of 1 to 2 D, 2.8 for astigmatism of 2 to 3 D, and 1.9 for astigmatism of 3 D or more. Anisometropia was associated significantly with unilateral amblyopia ($P < 0.0001$) in a dose-dependent manner, with an OR of 1.7 for 0.5 to 1.0 D, 4.3 for 1.0 to 2.0 D, and 9.2 for anisometropia of 2.0 D or more. Both esotropia and exotropia were associated similarly with unilateral amblyopia ($P < 0.0001$), with an OR of 3.2 for esotropia and 2.7 for exotropia, compared with children without strabismus.

The distributions of risk factors among the children with unilateral amblyopia are shown in Table 4. Among 296 children with unilateral amblyopia, 172 (58.1%) had either strabismus or anisometropia of 0.5 D or more, 97 (32.8%) only had either hyperopia (≥2 D) or astigmatism (≥1 D), and 27 (9.1%) had none of these risk factors.

Risk Factors for Bilateral Amblyopia

The results from the univariate analysis for demographic and ocular risk factors of bilateral amblyopia are shown in Table 5 (available at www.aaojournal.org). Age ($P = 0.69$), sex ($P = 0.45$), and race or ethnicity ($P = 0.44$) were not associated significantly with bilateral amblyopia. Astigmatism and significant refractive error (either spherical equivalent of >2.0 D or <0 D) were associated with a higher proportion of bilateral amblyopia ($P < 0.0001$). Further descriptive analyses showed that the proportion of children with bilateral amblyopia increased with the magnitude of bilateral astigmatism and bilateral hyperopia (Table 6, available at www.aaojournal.org; Fig 2).

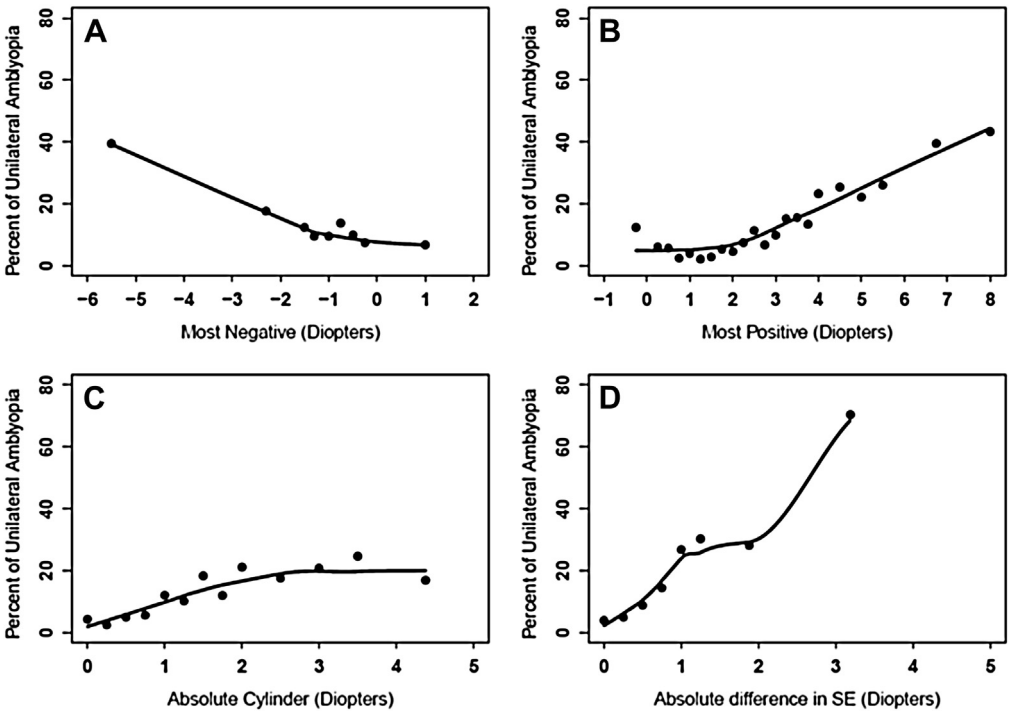

Figure 1. Graphs showing the percentage of unilateral amblyopia by various levels of refractive error (**A**) for myopia, (**B**) for hyperopia, (**C**) for astigmatism, and (**D**) for anisometropia. The refractive error in the most negative meridian of the most myopic eye was used for myopia; the most positive meridian of the most hyperopic eye was used for hyperopia; the absolute cylinder in the more astigmatic eye was used for astigmatism; and the interocular difference of spherical equivalent (SE) was used for anisometropia. The percentage of unilateral amblyopia by levels of refractive error was fitted by the locally weighted scatterplot smoothing curve.

In the multivariate analysis that considered age, astigmatism, and refractive error simultaneously (Table 7), astigmatism was associated independently with increased odds of bilateral amblyopia ($P < 0.0001$), with an OR of 3.3 for bilateral astigmatism of 1 to 2 D, 7.4 for bilateral astigmatism of 2 to 3 D, 20.9 for bilateral astigmatism of 3 to 4 D, and 17.7 for bilateral astigmatism of 4 D or more. Significant refractive errors (either myopia or bilateral hyperopia) were associated with higher risk of bilateral amblyopia. Compared with children with a spherical equivalent of 0 to 1 D in the most positive meridian of the less hyperopic eye, the children with myopia (<0.0 D in the most positive meridian) had a higher risk of bilateral amblyopia (OR, 9.6), and children with greater bilateral hyperopia had a higher risk of bilateral amblyopia, with an OR of 2.8 for bilateral hyperopia of 3 to 4 D and 5.0 for bilateral hyperopia of 4 D or more.

Among 144 children with bilateral amblyopia, 34 (23.6%) had hyperopic astigmatism (bilateral hyperopia ≥3 D and astigmatism ≥1 D), 22 (15.3%) had bilateral hyperopia (≥3 D) alone, 54 (37.5%) had astigmatism of 1 D or more alone, and 34 (23.6%) did not have any of these risk factors.

Discussion

This study evaluated demographic and ocular risk factors for both unilateral amblyopia and bilateral amblyopia among 3- to 5-year old preschoolers and quantified the magnitude of association with amblyopia for various severity levels of each type of refractive error. Our study revealed that the presence of strabismus (either esotropia or exotropia) and increasing severity of each type of refractive error (myopia, hyperopia, astigmatism, and anisometropia) were associated independently with increased odds of unilateral amblyopia. This study also found that bilateral astigmatism and bilateral hyperopia were associated independently with an increased risk of bilateral amblyopia.

Our results validated findings from previous population-based studies that established a strong association between refractive error and amblyopia in preschool children.[6,14] Furthermore, our study confirmed the dose-dependent relationship of refractive error with amblyopia, which was reported recently in the pooled analysis of data from the 2 largest population-based pediatric eye disease studies in the United States (MEPEDS and BPEDS).[14] Identification of the ocular risk factors and determination of their threshold levels associated with increased risk of amblyopia can be useful in identifying children at high risk for amblyopia through vision screening. In our study, we found that most (87%) unilateral amblyopia cases had significant refractive error (hyperopia ≥2.0 D, astigmatism ≥1.0 D, anisometropia ≥0.5 D). This is consistent with findings from other preschool studies that found refractive errors to be a major cause of amblyopia.[4,6,7] In the MEPEDS, 78% of children with amblyopia had significant refractive errors,[4] and in the Strabismus, Amblyopia and Refractive error in Singaporean Children Study, 85% of Chinese preschoolers with amblyopia had significant refractive error.[7]

Table 3. Multivariate Analysis for Risk Factors of Unilateral Amblyopia

Risk Factors	No.	Unilateral Amblyopia, n (%)	Odds Ratio (95% Confidence Interval)	P Value
Strabismus				<0.0001
No horizontal strabismus	3729	254 (6.8)	1.00	
Esotropia	91	33 (36.3)	3.24 (1.87–5.63)	<0.0001
Exotropia	49	9 (18.4)	2.74 (1.15–6.53)	0.02
Myopia in worse eye (D)				<0.0001
No	3429	230 (6.7)	1.00	
≥0.5 and <2.0	326	35 (10.7)	1.74 (1.08–2.80)	0.02
≥2.0	114	31 (27.2)	4.06 (2.18–7.56)	<0.0001
Hyperopia in worse eye (D)				<0.0001
No	2336	99 (4.2)	1.00	
≥2.0 and <3.0	909	65 (7.2)	1.75 (1.20–2.54)	0.004
≥3.0 and <4.0	302	39 (12.9)	2.46 (1.52–3.98)	0.0002
≥4.0 and <5.0	129	31 (24.0)	4.57 (2.63–7.95)	<0.0001
≥5.0	193	62 (32.1)	4.34 (2.54–7.42)	<0.0001
Astigmatism in worse eye (D)				<0.0001
No	2751	121 (4.4)	1.00	
≥1.0 and <2.0	710	94 (13.2)	2.17 (1.57–2.99)	<0.0001
≥2.0 and <3.0	269	51 (19.0)	2.81 (1.84–4.30)	<0.0001
≥3.0	139	30 (21.6)	1.88 (1.06–3.33)	0.03
Anisometropia (D)				<0.0001
No	2924	135 (4.6)	1.00	
≥0.5 and <1.0	714	77 (10.8)	1.65 (1.21–2.26)	0.002
≥1.0 and <2.0	151	50 (33.1)	4.26 (2.79–6.51)	<0.0001
≥2.0	62	34 (54.8)	9.16 (4.96–16.9)	<0.0001

D = diopters.

Anisometropia was found to be the major risk factor for amblyopia in the VIP study, with 161 children (54%) with unilateral amblyopic having anisometropia (≥0.5 D). In the multivariate analysis with adjustment for other ocular risk factors (strabismus, myopia, hyperopia, astigmatism), spherical equivalent anisometropia of 0.5 to 1.0 D was associated significantly with increased odds of unilateral amblyopia (OR, 1.7; $P = 0.002$), and the association became stronger with the increasing severity of anisometropia (OR of 4.3 for anisometropia of 1 to 2 D and 9.2 for anisometropia of 2 D or more; $P < 0.0001$ for all). These results supported findings that the risk of amblyopia is increased significantly with anisometropia of 1.0 D or more,[4,6,17–19] or even at lower threshold levels of anisometropia of 0.5 to 1.0 D.[14,20] Vector analysis of astigmatic anisometropia also suggested that interocular differences of J0 or J45 as low as 0.25 D are associated significantly with an increased risk of unilateral amblyopia.[14,20] These results demonstrated that the threshold at which anisometropia begins to be associated with amblyopia may be lower than the levels based on expert clinical opinion or those recommended by different professional organizations,[21–23] and screening for anisometropia also can help to identify a large portion of unilateral amblyopia cases.

Table 4. Composition of Risk Factors among Unilateral Amblyopia Cases (n = 296)

Composition of Risk Factors	No. (%)
Either anisometropia ≥0.5 D or strabismus, any degree of hyperopia, astigmatism or myopia	172 (58.1)
Anisometropia ≥0.5 D alone	130 (43.9)
Strabismus alone	11 (3.7)
Both anisometropia ≥0.5 D and strabismus	31 (10.5)
Only hyperopia or astigmatism	97 (32.8)
Hyperopia ≥2.0 D alone	22 (7.4)
Astigmatism ≥1.0 D alone	29 (9.8)
Hyperopia ≥2.0 D and astigmatism ≥1.0 D	46 (15.5)
None of above	27 (9.1)

D = diopters.

Significant hyperopia (>2.0 D) has been reported to be associated with an increased risk of amblyopia.[6] Our study further demonstrates that the association with unilateral amblyopia is severity dependent, with ORs ranging from 1.8 for hyperopia of 2 to 3 D to 4.3 for hyperopia of 4 D or more. Our study also demonstrated that increasing bilateral hyperopia is associated significantly with an increased risk of bilateral amblyopia, with ORs ranging from 2.8 for bilateral hyperopia of 3 to 4 D to 5.0 for hyperopia of 5 D or more. All these results were consistent with findings from large population-based, cross-sectional studies[6,14] and a longitudinal cohort study.[24] Screening for identification and correction of significant hyperopia (>2.0 D) in preschool children may be considered to reduce the risk of amblyopia. However, the optimal level of hyperopia that warrants the treatment needs further investigation.

Myopia is less common than hyperopia in preschool children, and its association with amblyopia has not been well studied. In this study, we found that myopia of 0.5 to

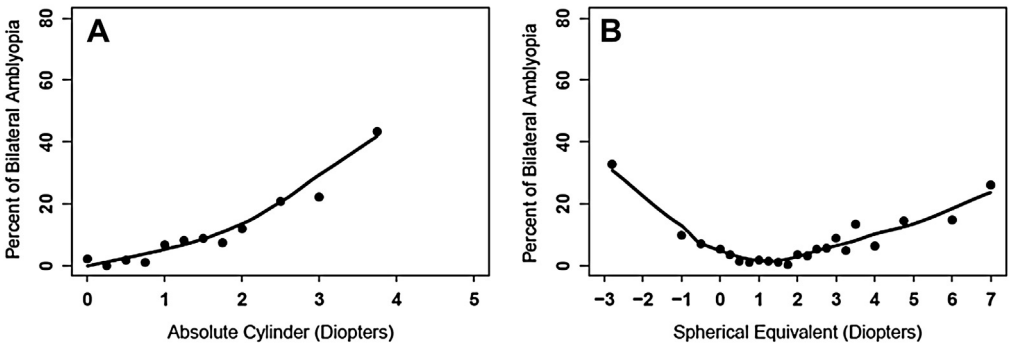

Figure 2. Graphs showing the percentage of bilateral amblyopia by various levels of refractive error for (**A**) astigmatism and (**B**) hyperopia. The absolute cylinder in the less astigmatic eye was used for astigmatism, and the spherical equivalent in the less hyperopic eye was used for hyperopia. The percentage of bilateral amblyopia by levels of refractive error was fitted by the locally weighted scatterplot smoothing curve.

2.0 D started to be associated with an increased risk of unilateral amblyopia (OR, 1.7) and that risk of unilateral amblyopia was increased further when myopia was 2.0 D or more (OR, 3.9) when compared with children without myopia (<0.5 D). The Sydney Pediatric Eye Disease Study (SPEDS) reported a similar OR (2.2) associated with myopia of 0.5 D or more, but the association was not statistically significant, which may be because of the small number of amblyopia cases in the study (n = 27; Table 8, available at www.aaojournal.org).[6] We also found that myopia was associated independently with an increased risk of bilateral amblyopia, with an OR of 9.6 compared with emmetropic children (0−1.0 D).

This study found that astigmatism of 1.0 D or more was associated with increased odds of unilateral amblyopia, but not in a dose-dependent manner in adjusted analysis (OR of 2.2 for astigmatism of 1 to 2 D, 2.8 for astigmatism of 2 to 3 D, and 1.9 for astigmatism >3 D, respectively). The SPEDS reported an OR of 5.7 for astigmatism of 1.0 D or more,[6] but this OR was not adjusted by other significant refractive error conditions (myopia, hyperopia, and anisometropia). In the VIP study, bilateral astigmatism (≥1 D) was associated with bilateral amblyopia, with an OR of 3.3 for bilateral astigmatism of 1 to 2 D, 7.4 for astigmatism of 2 to 3 D, and 20.9 for astigmatism of 3 D or more. This severity-dependent association was consistent with findings from the MEPEDS and BPEDS, which reported a significant OR of 2.3 for astigmatism of 1 to 2 D and 17.6 for astigmatism of 2 D or more.

The threshold levels of refractive error found to be associated with an increased risk of amblyopia are lower than the cutpoints recommended by professional organizations concerned with pediatric eye care, and our threshold levels for refractive error identified most (87%) unilateral amblyopia cases. The American Association for Pediatric Ophthalmology and Strabismus recommends the use of the following cutpoints for referral of amblyopia based on the screening of refractive error: spherical or cylindrical anisometropia of more than 1.5 D, hyperopia of more than 3.5 D in any meridian, myopia of more than 3.0 D in any meridian, and astigmatism of more than 1.5 D at 90° or 180° in the oblique axis.[23] Among 296 children with unilateral amblyopia in this study, only 173 (58.5%) had refractive error meeting the American Association for Pediatric Ophthalmology and Strabismus criteria. Among the 123 children with unilateral amblyopia in our study who did not met the American Association for Pediatric Ophthalmology and Strabismus criteria, 87 (70.7%) had an IAD of 2 lines, 26 (21.1%) had an IAD of 3 lines, 4 (3.3%) had an IAD of 4 lines, and 2 had an IAD of 5 to 6 lines. Some of these missed children had significant refractive error, including

Table 7. Multivariate Analysis for Risk Factors of Bilateral Amblyopia

Risk Factors	No.	Bilateral Amblyopia, n (%)	Odds Ratio (95% Confidence Interval)	*P* Value
Astigmatism in less astigmatic eye (D)				<0.0001
No	3135	56 (1.8)	1.00	
≥1.0 and <2.0	495	37 (7.5)	3.34 (2.14−5.22)	<0.0001
≥2.0 and <3.0	174	28 (16.1)	7.35 (4.37−12.4)	<0.0001
≥3.0 and <4.0	47	17 (36.2)	20.9 (10.3−42.3)	<0.0001
≥4.0	18	6 (33.3)	17.7 (5.86−53.5)	<0.0001
Refractive error in less hyperopic eye (D)				<0.0001
<0.0	159	26 (16.4)	9.55 (4.83−18.8)	<0.0001
≥0.0 and <1.0	805	15 (1.9)	1.00	
≥1.0 and <2.0	1746	19 (1.1)	0.59 (0.29−1.17)	0.13
≥2.0 and <3.0	695	28 (4.0)	1.56 (0.81−3.00)	0.18
≥3.0 and <4.0	252	24 (9.5)	2.81 (1.40−5.64)	0.004
≥4.0	212	32 (15.1)	5.04 (2.58−9.87)	<0.0001

D = diopters.

myopia of 0.5 D or more in 21 (17.9%), hyperopia of 2 D or more in 61 (49.6%), astigmatism of 1 D or more in 55 (44.7%), and anisometropia of 0.75 D or more in 22 (17.9%).

Strabismus is one of the well-known risk factors of amblyopia. However, it is uncertain whether esotropia or exotropia is associated equally with amblyopia, probably because of the limited number of cases (<100) for each type of strabismus in previous studies. In our study, esotropia was found to be associated with higher odds of unilateral amblyopia (OR, 7.8) than exotropia (OR, 3.1) when other risk factors were not accounted for. However, in a multivariate analysis with adjustment of refractive error and other risk factors, esotropia and exotropia had roughly equal ORs (3.2 and 2.7, respectively). The SPEDS also reported similar OR for esotropia and exotropia (ORs of 9.4 and 7.7, respectively, after adjusting for age, sex, ethnicity, and spherical equivalent).[6] However, data from the MEPEDS and BPEDS showed a very different risk of amblyopia for esotropia and exotropia. Esotropia was found to be associated significantly with amblyopia (OR, 9.0), whereas exotropia was not associated with amblyopia (OR, 1.2).[14] The exact association of esotropia and exotropia with amblyopia needs further investigation in a larger study.

Among the demographic characteristics (age, sex, race or ethnicity) we evaluated in this study, none were associated significantly with unilateral amblyopia. Overall, race or ethnicity was not associated with both unilateral amblyopia ($P = 0.19$) and bilateral amblyopia ($P = 0.44$) in univariate analysis. However, Hispanic ethnicity was found to be associated with higher odds of unilateral amblyopia (OR, 1.4; $P = 0.03$). Consistent with our results, the MEPEDS and BPEDS also found that Hispanic ethnicity was associated with a 2-fold greater odds of unilateral amblyopia when compared with non-Hispanic children.[14] The exact reason for the difference in amblyopia between Hispanic and non-Hispanic children is not known. It may be because of the difference in access to eye care, prior treatment, or genetic factors.

The strengths of this study include standardized comprehensive eye examinations performed by study-certified ophthalmologists and optometrists and a large sample of preschool children from a variety of racial and ethnic groups (black, Asian, Hispanic, non-Hispanic white, and American Indian) enrolled from 5 clinical centers across the United States. The enriched sample overrepresenting preschool children with vision disorders provided us with the largest number of unilateral amblyopia cases and bilateral amblyopia cases among large-scale studies (Table 8, available at www.aaojournal.org). This allowed us to evaluate ocular risk factors at several severity levels to determine the threshold levels associated with an increased risk of amblyopia.

Our study has several limitations. First, the VIP study was not designed as a population-based nor as a cohort study for evaluating risk factors of amblyopia. The VIP study was designed to overrepresent children with vision disorders; the absolute risk of amblyopia at each level of a risk factor is overestimated. However, the ORs estimated from the data are still valid and by definition are consistent with those estimated from population-based studies (Table 8, available at www.aaojournal.org). Second, all participants from the VIP study were preschoolers (3–5 years of age) enrolled from Head Start programs, a national, comprehensive child development program that serves low-income preschool children and their families. Because all of the children were from low-income families, our study findings may not apply to the general population if the relationship of risk factors to amblyopia is affected by family income level. However, this does not seem to be the case because the findings from the MEPEDS and BPEDS are very consistent with findings from the VIP study. Our study findings from 3- to 5-year-old children also may not apply to children of all ages. Third, not all the VAs for defining amblyopia were measured with best correction. The VIP study protocol did not require retesting a child with best correction when the IAD was fewer than 2 lines and the VA in each eye was in the normal range for the child's age. We classified these children as nonamblyopic under the assumption that the IAD would remain at fewer than 2 lines on retesting with best correction. We also excluded 160 children with an IAD of 2 lines or more who were not retested with correction (because their small amount of refractive error did not meet retest criteria). The children were retested with refraction on the same day instead of during a return visit with spectacle correction. These factors may bias the associations of risk factors with amblyopia in either direction. Finally, because the VIP study was not designed originally to evaluate the risk factors of amblyopia, the risk factors collected in the VIP study were not comprehensive. We evaluated only limited demographic characteristics and ocular risk factors of children. The MEPEDS and BPEDS[14] and the SPEDS[6] performed more comprehensive evaluations of risk factors, including demographic, clinical, behavioral, and ocular risk factors. However, these studies found only a child's age and ethnicity to be the significant demographic risk factors for amblyopia, along with established ocular risk factors. As a result, we do not think that the lack of evaluation of other potential risk could bias substantially the significant risk factors found in this study.

In summary, this study evaluated the demographic and ocular risk factors for unilateral amblyopia and for bilateral amblyopia in Head Start preschool children. The results of this study validated the risk factors for amblyopia identified from other large population-based studies and suggested that the threshold levels associated with increased risk of amblyopia may be lower than the thresholds recommended by professional organizations. The current guidelines for screening for amblyopia using refractive error may require re-evaluation in the general population to provide optimal criteria for identifying children at high risk for amblyopia.

References

1. Vision in Preschoolers Study Group. Comparison of preschool vision screening tests as administered by licensed eye care

professionals in the Vision in Preschoolers Study. Ophthalmology 2004;111:637–50.
2. US Preventive Services Task Force. Vision screening for children 1 to 5 years of age: US Preventive Services Task Force recommendation statement. Pediatrics 2011;127:340–6.
3. Williams C, Northstone K, Howard M, et al. Prevalence and risk factors for common vision problems in children: data from the ALSPAC study. Br J Ophthalmol 2008;92:959–64.
4. Multi-ethnic Pediatric Eye Disease Study Group. Prevalence of amblyopia and strabismus in African American and Hispanic children ages 6 to 72 months: the Multi-ethnic Pediatric Eye Disease Study. Ophthalmology 2008;115:1229–36.
5. Friedman DS, Repka MX, Katz J, et al. Prevalence of amblyopia and strabismus in white and African American children aged 6 through 71 months: the Baltimore Pediatric Eye Disease Study. Ophthalmology 2009;116:2128–34.
6. Pai AS, Rose KA, Leone JF, et al. Amblyopia prevalence and risk factors in Australian preschool children. Ophthalmology 2012;119:138–44.
7. Dirani M, Zhou B, Hornbeak D, et al. Prevalence and causes of decreased visual acuity in Singaporean Chinese preschoolers. Br J Ophthalmol 2010;94:1561–5.
8. Carlton J, Karnon J, Czoski-Murray C, et al. The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4–5 years: a systemic review and economic evaluation. Health Technol Asses 2008;12:iii,xi–94.
9. van Leeuwen R, Eijkemans MJ, Vingerling JR, et al. Risk of bilateral visual impairment in individuals with amblyopia: the Rotterdam study. Br J Ophthalmol 2007;91:1450–1.
10. Daw NW. Critical periods and amblyopia. Arch Opththalmol 1998;116:502–5.
11. Stewart CE, Fielder AR, Stephens DA, Moseley MJ. Treatment of unilateral amblyopia: factors influencing visual outcome. Invest Ophthalmol Vis Sci 2005;46:3152–60.
12. Williams C, Northsone K, Harrad RA, et al. Amblyopia treatment outcomes after screening before or at age 3 years: follow-up from randomised trial. BMJ 2002;324:1549.
13. Beauchamp GR. Chronic amblyopia and strabismus in children. Arch Ophthalmol 2007;125:821–2.
14. Tarczy-Hornoch K, Varma R, Cotter SA, et al; Joint Writing Committee for the Multi-Ethnic Pediatric Eye Disease Study and the Baltimore Pediatric Eye Disease Study Groups. Risk factors for decreased visual acuity in preschool children: the Multi-Ethnic Pediatric Eye Disease and Baltimore Pediatric Eye Disease studies. Ophthalmology 2011;118:2262–73.
15. Vision in Preschoolers Study Group. Preschool vision screening tests administered by nurse screeners compared with lay screeners in the Vision in Preschoolers Study. Invest Ophthalmol Vis Sci 2005;46:2639–48.
16. Holmes JM, Beck RW, Repka MX, et al; Pediatric Eye Disease Investigator Group. The Amblyopia Treatment Study visual acuity testing protocol. Arch Ophthalmol 2001;119:1345–53.
17. Weakley DR Jr. The association between nonstrabismic anisometropia, amblyopia, and subnormal binocularity. Ophthalmology 2001;108:163–71.
18. Weakley DR. The association between anisometropia, amblyopia, and binocularity in the absence of strabismus. Trans Am Ophthalmol Soc 1999;97:987–1021.
19. Dobson V, Miller JM, Clifford-Donaldson CE, Harvey EM. Associations between anisometropia, amblyopia, and reduced stereoacuity in a school-aged population with a high prevalence of astigmatism. Invest Ophthalmol Vis Sci 2008;49:4427–36.
20. Ying GS, Huang J, Maguire MG, et al; Vision in Preschoolers Study Group. Association of anisometropia with unilateral amblyopia, interocular acuity difference, and stereoacuity in preschoolers. Ophthalmology 2013;120:495–503.
21. American Academy of Ophthalmology Pediatric Ophthalmology/Strabismus Panel. Preferred Practice Pattern® Guidelines. Amblyopia. San Francisco, CA: American Academy of Ophthalmology.Available at: http://www.aao.org/ppp; 2012.Accessed August 12, 2013.
22. American Optometric Association Consensus Panel on Care of the Patient with Amblyopia. Optometric Clinical Practice Guideline. Care of the Patient with Amblyopia. St. Louis, MO: American Optometric Association.Available at: http://www.aoa.org/documents/CPG-4.pdf; 2004.Accessed April 22, 2013.
23. Donahue SP, Arnold RW, Ruben JB, AAPOS Vision Screening Committee. Preschool vision screening: what should we be detecting and how should we report it? Uniform guidelines for reporting results of preschool vision screening studies. J AAPOS 2003;7:314–6.
24. Colburn JD, Morrison DG, Estes RL, et al. Longitudinal follow-up of hypermetropic children identified during preschool vision screening. J AAPOS 2010;14:211–5.

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