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Risk Factors for Amblyopia in the Vision In Preschoolers Study

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Abstract

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, over-representing children with vision disorders.

Methods—All children underwent comprehensive eye exams 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 single-surround HOTV letter protocol without correction, and retested with full cycloplegic correction when retest criteria were met. Unilateral amblyopia was defined as an inter-ocular difference in best-corrected VA ≥ 2 lines. 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 (ORs) and their 95% confidence intervals (95% CIs) estimated from logistic regression models.

Results—In this enriched sample of Head Start children (N=3869), 296 (7.7%) children had unilateral amblyopia, and 144 (3.7%) children had bilateral amblyopia. Presence of strabismus ($p<0.0001$), greater magnitude of significant refractive errors (myopia, hyperopia, astigmatism,

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and anisometropia, each $p < 0.00001$) were independently associated with increased risk of unilateral amblyopia. Presence of strabismus, hyperopia 2.0 D, astigmatism 1.0 D, or anisometropia 0.5 D were present in 91% of children with unilateral amblyopia. Greater magnitude of astigmatism ($p < 0.0001$) and of bilateral hyperopia ($p < 0.0001$) were independently associated with increased risk of bilateral amblyopia. Bilateral hyperopia 3.0 diopters (D) or astigmatism 1.0 D were present in 76% of children with bilateral amblyopia.

Conclusion—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 study population, these results validated the findings from the Multi-ethnic Pediatric Eye Disease Study and Baltimore Pediatric Eye Disease Study.

INTRODUCTION

Vision disorders are the fourth most prevalent disability among children in the US 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 can also 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 in order 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 two 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 fully evaluated due to the limited number of amblyopia cases in most studies. A recent pooled report from the two largest U.S. population-based samples of preschool 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 levels 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 is lower than previously reported.¹⁴

The Vision In Preschoolers (VIP) Study is a multi-center study that over-sampled 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 the current report is 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 Vision In Preschoolers (VIP) Study. The VIP study is a multi-center 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 to 72 months) were enrolled from Head Start programs near the five VIP clinical centers across the US (Berkeley, California; Boston, Massachusetts; Columbus, Ohio; Philadelphia, Pennsylvania; 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 over represented. 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 paper 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, and/or significant refractive error. Anterior segment evaluation and dilated fundus examination were also 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 (EVA) system at 10 ft, 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 worse than 20/50 for 3-year-olds, VA worse than 20/40 for 4 to 5-year-olds, or there was an interocular acuity difference (IAD) ≥ 2 lines; and (2) hyperopia ≥ 2.0 diopters (D), or myopia ≥ 0.5 D, or astigmatism ≥ 1.0 D was present in either eye. 720 (18%) children in VIP Study met the retest criteria and were retested. The final visual acuity score of an eye was based on the best visual acuity score achieved from either initial test or retest.

Both a cover-uncover test and an alternating cover test were performed at distance (10 ft) 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 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 two principal meridians of each eye.

Amblyopia Determination

Unilateral amblyopia was defined as ≥ 2 lines 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 < 2

lines and VA in each eye was in the normal range for the child's age, these children were classified as non-amblyopic under the assumption that the IAD would remain <2 lines upon retesting. Children ($n=160$) with IAD ≥ 2 lines who were not re-tested with correction (because their small amount of refractive error did not meet retest criteria as defined above) 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 unilateral amblyopia in the analysis for risk factors of unilateral amblyopia, and was classified as bilateral amblyopia in the analysis for risk factors of bilateral amblyopia.

Risk Factors

In the VIP Study, demographic information (birth date, gender, 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/ethnicity was classified as American Indian, Asian, Black, non-Hispanic White, Hispanic, and other/unknown (for those reported with more than one race categories or those without race information). Age was calculated as the difference between date of comprehensive eye examination and birth date, and was grouped as 36–47 months, 48–59 months, and 60–72 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 other studies.^{6,14} For the ocular risk factors of unilateral amblyopia, we determined each type of refractive error based on the worse eye, as we assumed that the ocular condition in the worse eye dominated the association with unilateral amblyopia. We classified presence and severity levels for myopia (<0.5 D, 0.5 to <2 D, ≥ 2 D), hyperopia (<2 D, 2 to <3 D, 3 to <4 D, 4 to <5 D, 5 to <6 D, ≥ 6 D), astigmatism (<1 D, 1 to <2 D, 2 to <3 D, 3 to <4 D, ≥ 4 D), and spherical equivalent anisometropia (<0.5 D, 0.5 to <1 D, 1 to <2 D, ≥ 2 D). For the ocular risk factors of bilateral amblyopia, we defined bilateral astigmatism and bilateral hyperopia based on 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 non-significant 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 (95% CI) for each of the significant risk factor were calculated from the final multivariate logistic regression model.

To further explore 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 was then fitted by the locally weighted scatterplot smoothing (LOWESS) curve.

After the significant risk factors for unilateral amblyopia and bilateral amblyopia were determined, the composition of significant risk factors were 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 v9.2 (SAS Institute Inc., NC, Cary). Two sided p-values <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 (4.0%) children were excluded because of having an interocular difference of 2 lines or more but were not re-tested since their refractive error did not meet retest criteria. Additional 11 children (0.2%) were excluded due to missing refractive error measurements. As a result, the remaining 3869 subjects were analyzed for this paper.

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. Gender was equally distributed. Approximately half (51%) were African American, 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 on 3869 preschoolers, over-representing children with ocular conditions, 91 (2.4%) had esotropia, 49 (1.3%) had exotropia; 440 (11.3%) preschoolers had myopia of 0.5 D, 1533 (39.6%) had hyperopia of 2.0 D, 1118 (28.9%) had astigmatism 1.0 D in either eye, and 927 (24.0%) had any anisometropia 0.5 D. 734 (19.0%) children had astigmatism 1.0 D in both eyes, and 1159 (30.0%) had bilateral hyperopia 2.0 D. 296 (7.7%) children had unilateral amblyopia and 144 (3.7%) children had bilateral amblyopia. Twenty-three (0.6%) children 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 <http://aaojournal.org>). In children aged 36 to 72 months, age was not associated with unilateral amblyopia ($P=0.69$). Overall, race/ethnicity was not associated with unilateral amblyopia ($P=0.19$), however, the proportion of 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 significantly associated 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 <http://aaojournal.org>, Figure 1).

Table 3 provides multivariate analysis results for significant risk factors of unilateral amblyopia. Myopia was associated with unilateral amblyopia ($P<0.0001$). As compared with non-myopic children (<0.5 D), the OR was 1.7 for myopia 0.5 to 2.0 D, and 4.1 for myopia 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 2 to 3 D, 2.5 for hyperopia between 3 to 4 D, 4.6 for hyperopia 4 to 5 D, and 4.3 for hyperopia of 5.0 D or greater. Astigmatism was

significantly associated 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 greater. Anisometropia was significantly associated with unilateral amblyopia ($P<0.0001$) in a dose-dependent manner, with 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 2.0 D or greater. Both esotropia and exotropia were similarly associated with unilateral amblyopia ($P<0.0001$), with an OR of 3.2 for esotropia and 2.7 for exotropia, as compared to 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%) children had either strabismus or anisometropia of 0.5 D or greater, 97 (32.8%) only had either hyperopia (≥ 2 D) or astigmatism (≥ 1 D), and 27 (9.1%) children 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 <http://aaojournal.org>). Age ($P=0.69$), gender ($P=0.45$), and race/ethnicity ($P=0.44$) were not significantly associated with bilateral amblyopia. Astigmatism and significant refractive error (either spherical equivalent >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 <http://aaojournal.org>, and Figure 2).

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

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

DISCUSSION

This study evaluated demographic and ocular risk factors both for unilateral amblyopia and for 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 presence of strabismus (either esotropia or exotropia), and increasing severity of each type of refractive error (myopia, hyperopia, astigmatism, and anisometropia) were independently associated with increased odds of unilateral amblyopia. This study also found that bilateral astigmatism and bilateral hyperopia were independently associated with 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 recently reported in the pooled analysis of data from the two largest population-based pediatric eye disease studies in the US (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 majority (87%) of 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 which found refractive errors to be a major cause of amblyopia.^{4,6,7} In the MEPEDS study, 78% of children with amblyopia had significant refractive errors,⁴ and in the Strabismus, Amblyopia and Refractive error in Singaporean Children Study (STARS), 85% of Chinese preschoolers with amblyopia had significant refractive error.⁷

Anisometropia was found to be the major risk factor for amblyopia in the VIP Study, with 161 (54%) of unilateral amblyopic children 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 significantly associated with increased odds of unilateral amblyopia (OR=1.7, P=0.002), and the association became stronger with the increasing severity of anisometropia (odds ratio of 4.3 for anisometropia 1 to 2 D, and 9.2 for anisometropia 2 D or greater, all P<0.0001). These results supported findings from that the risk of amblyopia is significantly increased at anisometropia ≥ 1.0 D^{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 significantly associated 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 recommended by different professional organizations,^{21–23} and screening for anisometropia can also help identify a large portion of unilateral amblyopia.

Significant hyperopia (>2.0 D) has been reported to be associated with increased risk of amblyopia.⁶ Our study further demonstrates that the association with unilateral amblyopia is severity-dependent, with odds ratios ranging from 1.8 for hyperopia of 2 to 3 D, to 4.3 for hyperopia of 4 D or greater. Our study also demonstrated that increasing bilateral hyperopia is significantly associated with increased risk of bilateral amblyopia, with odds ratio ranging from 2.8 for bilateral hyperopia of 3 to 4 D, to 5.0 for hyperopia of 5 D or greater. All these results were consistent with findings from large population-based cross-sectional studies^{6,14} and the 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 myopia of 0.5 to 2.0 D started to be associated with increased risk of unilateral amblyopia (odds ratio of 1.7), and risk of unilateral amblyopia is further increased when myopia is 2.0 D or more (odds ratio of 3.9), when compared with children without myopia (<0.5 D). The Sydney Pediatric Eye Disease Study (SPEDS) reported similar odds ratio (2.2) associated with myopia 0.5 D or more, but the association was not statistically significant, which may be due to the small number of amblyopia cases in the study (n=27, Table 8, available at <http://aaojournal.org>).⁶ We also found that myopia was independently associated with an increased risk of bilateral amblyopia, with odds ratio of 9.6 as compared with emmetropic children (0 to 1.0 D).

This study found that astigmatism 1.0 D or greater was associated with increased odds of unilateral amblyopia but not in a dose-dependent manner in adjusted analysis (odds ratio 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 the odds ratio of 5.7 for astigmatism of 1.0 D or more,⁶ but this odds ratio 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 odds ratio of 3.3 for bilateral astigmatism of 1 to 2 D, 7.4 for astigmatism of 2 to 3 D, 20.9 for astigmatism of 3 D or more. This severity-dependent association was consistent with findings from MEPEDS/BPEDS that reported a significant odds ratio of 2.3 for astigmatism of 1 to 2 D, and 17.6 for astigmatism of 2 D or greater.

The threshold levels of refractive error found to be associated with 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 the majority (87%) of unilateral amblyopia cases. The AAPOS recommends the use of the following cutpoints for referral of amblyopia based on the screening of refractive error: spherical or cylindrical anisometropia > 1.5 D, hyperopia >3.5 D in any meridian, myopia >3.0 D in any meridian, astigmatism >1.5 D at 90° or 180° in oblique axis).²³ Among 296 children with unilateral amblyopia in this study, only 173 (58.5%) had refractive error meeting the AAPOS criteria. Among the 123 children with unilateral amblyopia in our study who did not meet the AAPOS criteria, 87 (70.7%) children had interocular acuity difference (IAD) of 2-lines, 26 (21.1%) had IAD of 3-lines, 4 (3.3%) had IAD of 4-lines, and 2 children had IAD of 5- to 6-lines. Some of these missed children had significant refractive error including myopia of 0.5 D or greater in 21 (17.9%) children, hyperopia of 2 D or greater in 61 (49.6%) children, astigmatism of 1 D or greater in 55 (44.7%) children, and anisometropia of 0.75 D or greater in 22 (17.9%) children.

Strabismus is one of the well-known risk factors of amblyopia. However, it is uncertain whether esotropia or exotropia is equally associated with amblyopia, probably due to 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 odds ratios (3.2 and 2.7 respectively). The SPEDS also reported similar odds ratio for esotropia and exotropia (odds ratios of 9.4, 7.7 respectively, after adjusting for age, gender ethnicity and spherical equivalent).⁶ However, data from the MEPEDS/BPEDS showed a very different risk of amblyopia for esotropia and exotropia. Esotropia was found to be significantly associated with amblyopia (odds ratio of 9.0), while exotropia was not associated with amblyopia (odds ratio of 1.2).¹⁴ The exact association of esotropia and exotropia with amblyopia needs further investigation in a larger study.

Among the demographic characteristics (age, gender, race/ethnicity) we evaluated in this study, none of them were significantly associated with unilateral amblyopia. Overall, race/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 (odds ratio of 1.4, p=0.03). Consistent with our results, MEPEDS/BPEDS also found that Hispanic ethnicity was associated with two-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 due to the difference in the 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 (African American, Asian, Hispanic, non-Hispanic White, and American Indian) enrolled from five clinical centers across the United States. The enriched sample over-representing of preschool children with vision disorders provided us with largest number of unilateral amblyopia cases and bilateral amblyopia cases among large-scale studies (Table 8, available at <http://aaojournal.org>). This allowed us to evaluate ocular risk factors at several severity levels to determine the threshold levels associated with 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 over-represent children with vision disorders, the absolute risk of amblyopia at each level of a risk factor is over-estimated. However, the odds ratios estimated from the data are still valid, and by definition are consistent with those estimated from population-based studies (Table 8, available at <http://aaojournal.org>). Second, all participants from the VIP Study were preschoolers (3- to 5-years old) 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 appear to be the case because the findings from MEPEDS/BPEDS are very consistent with findings from the VIP Study. Our study findings from 3- to 5-years old children may also not apply to children of all ages. Third, not all the visual acuities for defining amblyopia were measured with best correction. VIP Study protocol did not require retesting a child with best correction when the IAD was <2 lines and VA in each eye was in the normal range for the child's age. We classified these children as non-amblyopic under the assumption that the IAD would remain <2 lines upon retesting with best correction. We also excluded 160 children with IAD ≥ 2 lines who were not re-tested 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 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 originally designed to evaluate the risk factors of amblyopia, the risk factors collected in the VIP Study were not comprehensive. We only evaluated limited demographic characteristics and ocular risk factors of children. The MEPEDS/BPEDS Studies¹⁴ and SPEDS⁶ performed more comprehensive evaluations of risk factors including demographic, clinical, behavioral and ocular risk factors. However, these studies only found child's age and ethnicity to be the significant demographic risk factors of amblyopia, along with established ocular risk factors. As a result, we do not think the lack of evaluation of other potential risk could substantially bias 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 validate the risk factors for amblyopia identified from other large population-based studies, and suggest 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 general population to provide optimal criteria for identifying children at high risk for amblyopia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The percent of unilateral amblyopia by various levels of refractive error for myopia (A), hyperopia (B), Astigmatism (C) and Anisometropia (D) was presented. The refractive error in the most negative meridian of the most myopic eye was used for myopia; 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 inter-ocular difference of spherical equivalent (SE) was used for anisometropia. The percent of unilateral amblyopia by levels of refractive error was fitted by the locally weighted scatterplot smoothing (LOWESS) curve.

Figure 2.

The percent of bilateral amblyopia by various levels of refractive error for astigmatism (**A**), hyperopia (**B**) was presented. The absolute cylinder in the less astigmatic eye was used for astigmatism; and the spherical equivalent (SE) in the less hyperopic eye was used for hyperopia. The percent of bilateral amblyopia by levels of refractive error was fitted by the locally weighted scatterplot smoothing (LOWESS) curve.

Table 3

Multivariate Analysis for Risk Factors of Unilateral Amblyopia

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

D = Diopter.

Table 4

Composition of Risk Factors among Unilateral Amblyopia Cases (N=296)

Composition of Risk Factors	n (%)
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 31.0 D	46 (15.5%)
None of above	27 (9.1%)

D = Diopter.

Table 7

Multivariate Analysis for Risk Factors of Bilateral Amblyopia

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

D = Diopter.