Risk Factors Associated with Childhood Strabismus

The Multi-Ethnic Pediatric Eye Disease and Baltimore Pediatric Eye Disease Studies

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Objective: To investigate risk factors associated with esotropia or exotropia in infants and young children.

Design: Population-based cross-sectional prevalence study.

Participants: Population-based samples of 9970 children 6 to 72 months of age from California and Maryland.

Methods: Participants were preschool African-American, Hispanic, and non-Hispanic white children participating in the Multi-Ethnic Pediatric Eye Disease Study and the Baltimore Eye Disease Study. Data were obtained by parental interview and ocular examination. Odd ratios and 95% confidence intervals were calculated to evaluate the association of demographic, behavioral, and clinical risk factors with esotropia and exotropia.

Main Outcome Measures: Odds ratios (ORs) for various risk factors associated with esotropia or exotropia diagnosis based on cover testing.

Results: In multivariate logistic regression analysis, esotropia was associated independently with prematurity, maternal smoking during pregnancy, older preschool age (48–72 months), anisometropia, and hyperopia. There was a severity-dependent association of hyperopia with the prevalence of esotropia, with ORs increasing from 6.4 for 2.00 diopters (D) to less than 3.00 D of hyperopia, to 122.0 for 5.00 D or more of hyperopia. Exotropia was associated with prematurity, maternal smoking during pregnancy, family history of strabismus, female sex, astigmatism (OR, 2.5 for 1.50 to $<$2.50 D of astigmatism, and 5.9 for $\geq$2.5 D of astigmatism), and anisoastigmatism in the J0 component (OR, $\geq$2 for J0 anisoastigmatism of $\geq$0.25 D).

Conclusions: Prematurity and maternal smoking during pregnancy are associated with a higher risk of having esotropia and exotropia. Refractive error is associated in a severity-dependent manner to the prevalence of esotropia and exotropia. Because refractive error is correctable, these risk associations should be considered when developing guidelines for the screening and management of refractive error in infants and young children.

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Strabismus, a manifest misalignment of the eyes, is a common childhood ocular disorder that often results in vision loss from amblyopia and impaired binocular depth perception. In addition to the functional effects of strabismus, there are often aesthetic concerns that can contribute to psychosocial difficulties in terms of self-image,[1–3] interpersonal relationships,[4] and social prejudice.[5–7] Many patients with strabismus undergo surgical correction or lengthy therapy in hopes of improved ocular alignment, attainment of better sensorimotor fusion, or both.

Only recently have population-based age- and ethnicity-specific prevalence estimates for strabismus become available for young children in the United States, with overall rates among different ethnic groups ranging from 2.1% to 3.3% in children younger than 6 years.[8,9] The cause of childhood strabismus is not well understood, but

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it is likely that both genetic and environmental factors contribute.

Various early life factors, such as hyperopia,[10] have been reported or postulated to be associated with strabismus, yet there is limited contemporary population-based data that have explored the effect of these influences on the development of childhood strabismus while controlling for confounding risk factors. Identifying risk factors for strabismus, especially modifiable ones, has public health significance. This is particularly important in view of the potential long-term consequences of vision loss and depth perception, as well as the psychosocial ramifications of persistent strabismus.[1–7]

Eye care providers long have been aware of an association between refractive error and certain forms of strabismus. For example, refractive accommodative esotropia, the most prevalent type of esotropia in the United States,[11,12] is a well-characterized consequence of childhood hyperopia.[13,14] However, the degree of increased risk associated with different degrees of hyperopia and the extent to which other types of ametropia pose a risk for strabismus are not known. Defining these relationships is important in that it can help to guide eye care providers in the management of childhood refractive error, to inform developers of refractive error-based screening instruments as to the thresholds of refractive error that need to be detected, and to influence public health policy makers with regard to refractive error-based screening referral thresholds. Using population-based data to establish the level of risk is preferable to using data derived from clinical populations because of the inherent referral bias and overrepresentation of disease found in clinical centers. The objective of the present study was to quantify risk associations, particularly refractive error, for horizontal strabismus in an ethnically diverse cohort of children 6 to 72 months of age enrolled in the population-based Multi-Ethnic Pediatric Eye Disease Study (MEPEDS) and Baltimore Pediatric Eye Disease Study (BPEDS).

Methods

The study population comprised 9970 participants 6 to 72 months of age enrolled in 1 of 2 population-based cross-sectional studies: the MEPEDS in southern California and the BPEDS in and around the city of Baltimore, Maryland. The study population, recruitment, cross-site standardization and certification procedures, and an overview of the interview and ocular examination, including details of cycloplegic refraction procedures, are described in a companion article[15] and in prior publications.[16,17] A parent or guardian of each participant gave written informed consent. The institutional review board, ethics, privacy, and study oversight statements for this report are identical to the statements in a companion paper.[15] Methodologic details specific to the present study are included herein.

Clinic Interview and Ocular Examination

Trained interviewers conducted standardized parental interviews in the clinic and optometrists or ophthalmologists, trained and certified using standardized protocols, conducted comprehensive eye examinations.[15–17] The ocular examination, described in detail elsewhere,[8,16,17] included monocular distance visual acuity testing for children 30 months of age and older, using single-surrounded HOTV optotypes on the Electronic Visual Acuity Tester (EVA)[18] according to the Amblyopia Treatment Study protocol,[19] using naming or matching of letters[20,21]; fixation preference testing[22,23]; evaluation of ocular alignment; anterior segment and dilated fundus evaluations; and measurement of refractive error under cycloplegic conditions.[15] Vector analysis was used to determine the J0 (power in the vertical or horizontal meridian) and J45 (power in the oblique meridian) vector components of astigmatism.[24,25]

Determination of Strabismus

Ocular alignment was evaluated using the unilateral cover (cover–uncover) test and alternate cover and prism test, at distance and near fixation, without correction and with optical correction, if worn. Transient misalignment after alternate cover testing was not designated as strabismus unless confirmed by a repeat unilateral cover test. Strabismus was classified according to the primary direction (esotropia, exotropia, vertical) of the tropia. Hirschberg testing was used when cover testing could not be performed. Strabismus was defined as constant or intermittent heterotropia of any magnitude at distance or near fixation, or both. Children tested at only 1 fixation distance and found to be without strabismus were considered nonstrabismic.

Statistical Analysis

Potential risk factors were based on previously reported associations with strabismus or plausible prior hypotheses. Demographic, behavioral, and clinical factors evaluated for each child are detailed in a companion article[15] and are found in Table 1. Ocular risk factors were bilateral spherical equivalent (SE) refractive error (SE of less hyperopic eye), bilateral astigmatism (absolute astigmatism of less astigmatic eye), SE anisometropia, J0 anisometropia (interocular difference in J0), and J45 anisometropia (interocular difference in J45); the dioptric criteria for levels of magnitude are provided in Table 2. The less hyperopic eye was chosen for SE refractive error analysis because if anisometropia is present, accommodative convergence (a potential contributor to convergent strabismus) is likely to be driven by accommodation in the less hyperopic eye.

Risk factors were explored separately for esotropia and exotropia using univariate analysis; those showing at least marginally significant associations ($P<0.1$) were considered candidates for subsequent forward stepwise multiple logistic regression (except for Down syndrome and cerebral palsy, because of small numbers, and family history of strabismus or amblyopia, because of questionable accuracy of parental report). If family history was significant at the univariate level, the sensitivity of the final multivariate model to the addition of family history to the model was explored. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for significant independent risk factors included in the final model. Univariate results are reported using the same restricted data set as the final model; participants with missing values for any variable included in the final multivariate model were excluded. Formal tests of interaction between selected variables were completed by including a product term in the multivariate model. Further details regarding the statistical analyses and regarding the locally weighted scatterplot smoothing (LOWESS) technique[26] used to examine the independent relationship between continuous risk factors and the prevalence of esotropia and exotropia are provided in a companion article.[15]

Table 1. Frequency Distributions of Demographic, Behavioral, and Clinical Risk Factors in Children with and without Strabismus in the Multi-Ethnic Pediatric Eye Disease Study and the Baltimore Pediatric Eye Disease Study

Risk Factor	Esotropia (n = 102), n (%)*	No Esotropia (n = 8389), n (%)*	*P* Value†	Exotropia (n = 102), n (%)*	No Exotropia (n = 8389), n (%)*	*P* Value†
Age group (mos)			<0.0001			0.03
06–11	2 (0.3)	796 (99.7)		7 (0.9)	791 (99.1)	
12–23	10 (0.7)	1485 (99.3)		10 (0.7)	1485 (99.3)	
24–35	13 (0.8)	1541 (99.2)		14 (0.9)	1540 (99.1)	
36–47	16 (1.1)	1512 (98.9)		20 (1.3)	1508 (98.7)	
48–59	29 (1.9)	1533 (98.1)		30 (1.9)	1532 (98.1)	
60–72	32 (2.1)	1522 (97.9)		21 (1.4)	1533 (98.6)	
Female sex	48 (1.2)	4060 (98.8)	0.79	61 (1.5)	4047 (98.5)	0.02‡
Race/ethnic group			0.03			0.61
Non-Hispanic white	33 (1.8)	1828 (98.2)		20 (1.1)	1841 (98.9)	
African-American	41 (1.1)	3563 (98.9)		41 (1.1)	3563 (98.9)	
Hispanic	28 (0.9)	2998 (99.1)		41 (1.4)	2985 (98.6)	
Study site			0.96			0.52
MEPEDS	78 (1.2)	6435 (98.8)		81 (1.2)	6432 (98.8)	
BPEDS	24 (1.2)	1954 (98.8)		21 (1.1)	1957 (98.9)	
Caregiver education <high school diploma/GED§	25 (1.0)	2385 (99.0)	0.35	33 (1.4)	2377 (98.6)	0.41
Household income <$20000/yr§	59 (1.4)	4137 (98.6)	0.16	55 (1.3)	4141 (98.7)	0.19
Health insurance§	95 (1.2)	8049 (98.8)	0.13	97 (1.2)	8047 (98.8)	0.60
Vision insurance§	65 (1.6)	3971 (98.4)	0.003	47 (1.2)	3989 (98.8)	0.41
Last routine medical examination <2 yrs§	101 (1.2)	8232 (98.8)	0.38	99 (1.2)	8234 (98.8)	0.37
Limited access to health care§	16 (1.4)	1155 (98.6)	0.56	18 (1.5)	1153 (98.5)	0.32
Smoking during pregnancy	19 (2.6)	725 (97.4)	0.0004	23 (3.1)	721 (96.9)	<0.0001
Alcohol use during pregnancy§	3 (1.2)	252 (98.8)	1.000	5 (2.0)	250 (98.0)	0.24
History of breastfeeding§	59 (1.0)	5634 (99.0)	0.06	59 (1.0)	5634 (99.0)	0.05
Maternal age at childbirth ≥35 yrs§	17 (1.6)	1042 (98.4)	0.20	17 (1.6)	1042 (98.4)	0.20
Gestational age (wks)†			0.0002‖			0.01‖
<33	11 (4.4)	237 (95.6)		8 (3.2)	240 (96.8)	
33–<37	9 (1.6)	540 (98.4)		9 (1.6)	540 (98.4)	
37–<42	78 (1.1)	7261 (98.9)		81 (1.1)	7258 (98.9)	
≥42	4 (1.1)	351 (98.9)		4 (1.1)	351 (98.9)	
Small for gestational age§	16 (1.0)	1567 (99.0)	0.55	21 (1.3)	1562 (98.7)	0.65
Down syndrome§	1 (6.3)	15 (93.7)	0.18	0 (0.0)	16 (100.0)	1.00
Cerebral palsy§	2 (16.7)	10 (83.3)	0.009	3 (25.0)	9 (75.0)	0.0003
Family history of strabismus§	15 (2.9)	496 (97.1)	0.0002	14 (2.7)	497 (97.3)	0.0006
Family history of amblyopia§	2 (1.7)	116 (98.3)	0.61	3 (2.5)	115 (97.5)	0.17

BPEDS = Baltimore Pediatric Eye Disease Study; GED = General Educational Development test; MEPEDS = Multi-Ethnic Pediatric Eye Disease Study.
*Percentage of participants with stated level of risk factor.
†Chi-square or Fisher exact test where applicable.
‡Sex was associated with exotropia at the univariate level only in the restricted, final model data set, not in the overall data set, and therefore was not considered in the final model in the primary analysis.
§Denominators (number of participants with stated outcome status) for this variable differ from other variables because of missing data.
‖*P* value for dichotomous categorization (<33 wks; ≥33 wks).

Results

Eighty percent of eligible MEPEDS children and 62% of eligible BPEDS children were examined. Comparison of participants and nonparticipants has been published previously.[8,17] The study population comprised 9970 children who underwent clinical examination (Fig 1). Of these, 4849 (49%) were girls; 4355 (43.7%) were African-American, 3147 (31.6%) were Hispanic, and 2468 (24.8%) were non-Hispanic white. The multivariate models were based on 8491 participants with complete data for all significant variables (Fig 1), including 102 children with esotropia and 102 with exotropia. There were no significant differences in characteristics of children included in the data analysis compared with those excluded for missing data except for the sex of those with exotropia ($P = 0.02$). Of those excluded, 2.2% of the boys and 1.2% of the girls had exotropia (difference was not significant; $P = 0.16$), in contrast to those analyzed, among whom 0.9% of boys and 1.5% of girls had exotropia. In the MEPEDS, only 19% of strabismic children had ever been treated for strabismus, and in the BPEDS,[9] only 27% had been treated previously. The demographic, behavioral, clinical, and refractive error characteristics for those with and without esotropia and those with and without exotropia are provided in Tables 1 and 2.

Esotropia

The univariate analysis results for associations between potential risk factors evaluated and esotropia are provided in Tables 1 and 2. After adjustment for the other variables in the multivariate analysis, the following were identified as independent indicators of a

Table 2. Frequency Distributions of Refractive Error Risk Factors in 6- to 72-Month-Old Children with and without Strabismus in the Multi-Ethnic Pediatric Eye Disease Study and the Baltimore Pediatric Eye Disease Study

Risk Factor	Esotropia (n = 102), n (%)*	No Esotropia (n = 8389), n (%)*	*P* Value§	Exotropia (n = 102), n (%)*	No Exotropia (n = 8389), n (%)*	*P* Value§
SE anisometropia (D)			<0.0001			0.004
<0.50	64 (1.0)	6546 (99.0)		72 (1.1)	6538 (98.9)	
0.50–<1.00	21 (1.4)	1496 (98.6)		19 (1.3)	1498 (98.7)	
≥1.00	17 (4.7)	347 (95.3)		11 (3.0)	353 (97.0)	
J0 anisometropia (D)			0.03			<0.0001
<0.25	74 (1.1)	6938 (98.9)		67 (1.0)	6945 (99.0)	
0.25–<0.50	23 (1.9)	1165 (98.1)		26 (2.2)	1162 (97.8)	
≥0.50	5 (1.7)	286 (98.3)		9 (3.1)	282 (96.9)	
J45 anisometropia (D)			0.007			<0.0001
<0.25	68 (1.0)	6623 (99.0)		72 (1.1)	6619 (98.9)	
0.25–<0.50	20 (1.7)	1150 (98.3)		10 (0.9)	1160 (99.1)	
≥0.50	14 (2.2)	616 (97.8)		20 (3.2)	610 (96.8)	
Astigmatism† (D)			<0.0001			<0.0001
<0.50	44 (0.9)	5148 (99.1)		49 (0.9)	5143 (99.1)	
0.50–<1.00	26 (1.3)	2020 (98.7)		19 (0.9)	2027 (99.1)	
1.00–<1.50	18 (2.6)	685 (97.4)		13 (1.9)	690 (98.1)	
1.50–<2.50	12 (2.9)	407 (97.1)		12 (2.9)	407 (97.1)	
≥2.50	2 (1.5)	129 (98.5)		9 (6.9)	122 (93.1)	
SE refractive error† (D)			<0.0001‡			0.001‡
≥−1.00	3 (0.8)	398 (99.2)		13 (3.2)	388 (96.8)	
−1.00–<0.00	5 (0.5)	1007 (99.5)		14 (1.4)	998 (98.6)	
+0.00–<+1.00	7 (0.2)	2907 (99.8)		34 (1.2)	2880 (98.8)	
+1.00–<+2.00	12 (0.5)	2651 (99.5)		29 (1.1)	2634 (98.9)	
+2.00–<+3.00	14 (1.5)	905 (98.5)		5 (0.5)	914 (99.5)	
+3.00–<+4.00	20 (5.7)	331 (94.3)		4 (1.1)	347 (98.9)	
+4.00–<+5.00	17 (13.1)	113 (86.9)		1 (0.8)	129 (99.2)	
+≥5.00	24 (23.8)	77 (76.2)		2 (2.0)	99 (98.0)	

BPEDS = Baltimore Pediatric Eye Disease Study; D = diopters; J0 = power in the vertical or horizontal meridian; J45 = power in the oblique meridian; MEPEDS = Multi-Ethnic Pediatric Eye Disease Study; SE = spherical equivalent.
*Percentage of participants with stated outcome status.
†Level of refractive error defined by the less hyperopic eye for SE refractive error, and the less astigmatic eye for astigmatic refractive error, or by the eye with refractive error data if data are missing for the fellow eye.
‡*P* value for esotropia analysis is reported using a single category for all SE refractive errors <0.00 D; *P* value for exotropia analysis is reported using a single category for all SE refractive errors ≥1.00 D.
§Chi square or Fisher exact test where applicable.

greater risk for esotropia: gestational age younger than 33 weeks (OR, 4.43), active maternal smoking during pregnancy (OR, 2.04), age range of 48 to 72 months (OR, ≥7.94 relative to reference age group of 6–11 months), SE anisometropia of 1.00 D or more (OR, 2.03 relative to reference level of <0.50 D), and SE hyperopia starting at the 2.00 to less than 3.00 D level (OR, 6.38–122.24 for different levels of hyperopia, relative to reference level of 0.00 to <+1.00 D; Table 3).

Having vision insurance also was associated with increased likelihood of esotropia (OR, 1.62; 95% CI, 1.03–2.55; adjusted for covariates listed above). However, because vision insurance likely was obtained as a consequence of having esotropia, rather than it causing esotropia, vision insurance was not included as a covariate in the final multivariate model. When vision insurance was included, the associations with other variables were qualitatively unchanged, with only minor differences in ORs.

When the sensitivity of the final model to adding the variable of positive family history of strabismus was explored, it was associated with greater odds of having esotropia (OR, 1.86); however, this association did not reach statistical significance ($P = 0.054$; 95% CI, 0.99–3.48), nor did it substantively alter the ORs of any other variable in the final model.

Hyperopia of 3.00 D or more was the strongest predictor of esotropia. The LOWESS plot (Fig 2) shows an approximately linear relationship between prevalence of esotropia and SE refractive error starting at a magnitude of hyperopia of 2.00 D and extending beyond, with an essentially flat plot for myopic, emmetropic, and hyperopic refractive error less than 2.00 D. The LOWESS plot of esotropia prevalence as a function of SE anisometropia shows an increase in risk of esotropia primarily for levels of anisometropia of more than 1.00 D (Fig 3, available at http://aaojournal.org).

To explore further the relationship between maternal smoking during pregnancy and esotropia, the estimated prevalence of esotropia was evaluated as a function of pack-months of smoking during pregnancy, adjusting for all other significant covariates in the final multivariate model. A LOWESS plot illustrating a linear relationship between amount of smoking and risk of esotropia is shown in Figure 4. The multivariate model also was run without including refractive error variables as covariates and found only a small increase in the OR for the association of esotropia with maternal smoking as a dichotomous variable (OR, 2.34; 95% CI, 1.41–3.89).

Including interaction variables in the multivariate model did not reveal any statistically significant interactions between the effects of SE refractive error and age or between the effects of SE refractive error and SE anisometropia with regard to increased risk of esotropia.

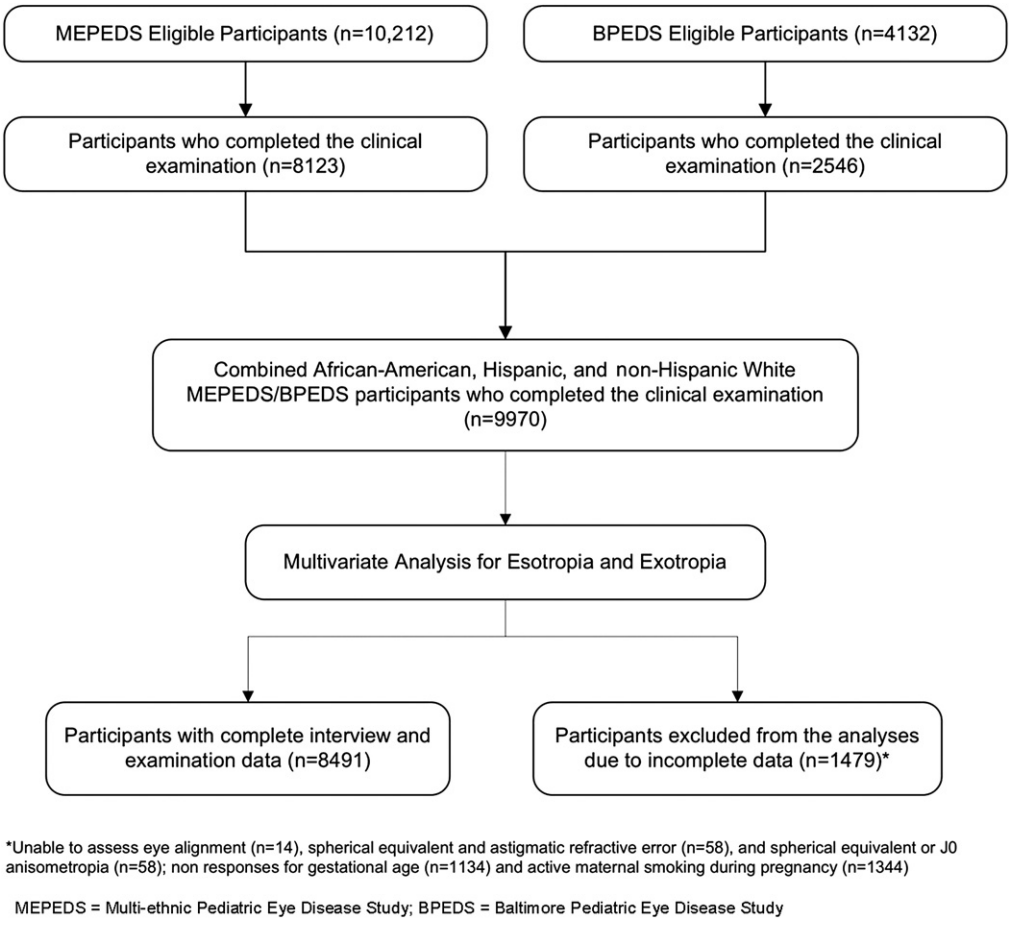

Figure 1. Participant flow chart showing children in the Multi-Ethnic Pediatric Eye Disease Study (MEPEDS) and the Baltimore Pediatric Eye Disease Study (BPEDS) cohorts who were included and excluded from the final analysis sample for both the esotropia and exotropia outcomes.

Subgroup analysis for the MEPEDS alone identified a very similar set of independent risk factors, with the following differences: maternal smoking was not independently associated with esotropia, whereas racial/ethnic group was associated with esotropia (OR, 2.84; 95% CI, 1.50–5.38 for non-Hispanic white children relative to the Hispanic reference group), as was lack of health insurance (OR, 3.71; 95% CI, 1.53–9.00). The subgroup analysis for BPEDS alone also yielded similar results, finding significant associations of esotropia with SE refractive error, age group, and maternal smoking, although analysis of BPEDS data did not reveal associations with SE anisometropia or gestational age.

Exotropia

The results of the univariate analysis of associations between potential risk factors and exotropia are shown in Tables 1 and 2. In the multivariate analysis, active maternal smoking during pregnancy, gestational age less than 33 weeks, female sex, bilateral astigmatism of 1.50 D or more, and J0 anisometropia of at least 0.25 to 0.50 D (equivalent to 0.50–1.00 D interocular difference in cylinder amount for a given axis of cylinder) were identified as independent indicators of a greater risk for exotropia after adjustment for the other variables (Table 4).

Astigmatism of 2.50 D or more was the strongest risk factor, conferring a 6-fold risk for exotropia. A LOWESS plot of the estimated prevalence of exotropia, adjusting for all other significant covariates, shows an approximately linear relationship with the magnitude of astigmatism (Fig 5). The estimated prevalence of exotropia also increased with increasing J0 anisometropia, up to approximately 1.00 D (Fig 6, available at http://aaojournal.org).

To explore further the relationship between maternal smoking during pregnancy and exotropia, the estimated prevalence of exotropia, adjusted for all other significant covariates in the final multivariate model, was evaluated as a function of pack-months of smoking during pregnancy. A LOWESS plot illustrating the linear relationship between amount of smoking and risk of exotropia is shown in Figure 4. The multivariate model also was run without refractive error variables as covariates and only a small increase in the OR was found for the association of exotropia with maternal smoking as a dichotomous variable (OR, 3.02; 95% CI, 1.89–4.85).

Subgroup analyses for MEPEDS alone identified the same set of independent risk factors for exotropia, as well as an increased risk of exotropia with SE myopia of 1.00 D or more in at least 1 eye (OR, 2.46; 95% CI, 1.17–5.16, relative to group having 0.00 to $<$1.00 D of SE refractive error in the less hyperopic eye). Subgroup analysis for the BPEDS alone showed an increased risk of exotropia with maternal smoking during pregnancy and gestational age, as well as 2 risk factors that were not significant in the combined analysis: being small for gestational age (OR, 4.08; 95% CI, 1.69–9.85) and lacking health insurance (OR, 4.95; 95% CI, 1.05–23.30).

When the sensitivity of the final model to adding the variable of positive family history of strabismus was explored, it was found to

Table 3. Independent Risk Factors* for Childhood Esotropia in 6- to 72-Month-Old Children in the Multi-Ethnic Pediatric Eye Disease Study and Baltimore Pediatric Eye Disease Study

Risk Factor	Odds Ratio (95% Confidence Interval)†	P Value
SE refractive error (D)		<0.0001
+0.00–<+1.00	Reference	
<0.00 (myopia)	2.48 (0.89–6.91)	
+1.00–<+2.00	1.81 (0.71–4.62)	
+2.00–<+3.00	**6.38 (2.56–15.93)**	
+3.00–<+4.00	**23.06 (9.56–55.61)**	
+4.00–<+5.00	**59.81 (23.61–151.52)**	
+≥5.00	**122.24 (49.86–299.70)**	
Gestational age <33 wks	**4.43 (2.14–9.19)**	<0.0001
Age group (mos)		0.0003
06–11	Reference	
12–23	2.88 (0.62–13.46)	
24–35	3.75 (0.83–17.04)	
36–47	4.03 (0.90–17.92)	
48–59	**7.94 (1.85–34.03)**	
60–72	**9.40 (2.20–40.10)**	
Maternal smoking during pregnancy	**2.04 (1.17–3.56)**	0.01
Spherical equivalent anisometropia (D)		0.05
<0.50	Reference	
0.50–<1.00	0.91 (0.53–1.55)	
≥1.00	**2.03 (1.10–3.73)**	

D = diopters; SE = spherical equivalent.
Odds ratios in boldface are statistically significant.
*Adjusted for all factors listed in the table.
†Based on multivariate stepwise logistic regression model.

be associated independently with a greater risk for exotropia (OR, 2.29; 95% CI, 1.27–4.13; $P = 0.006$). Adding this variable did not substantively alter the significance or the ORs of any of the other variables in the final model.

Discussion

The present study used a large population-based and ethnically diverse cohort of children 6 to 72 months of age to identify independent risk factors for childhood esotropia and exotropia. The major potentially modifiable or correctable risk factors for esotropia were hyperopic and anisometropic refractive error and maternal smoking during pregnancy; gestation less than 33 weeks and older age (range, 48–72 months) also conferred a higher risk. For exotropia, maternal smoking during pregnancy, shortened gestation, female sex, and family history of strabismus were independent risk factors, as was astigmatic refractive error and anisometropia with regard to the J0 component of astigmatism.

Maternal smoking during pregnancy was associated with both esotropia and exotropia. Among previous studies,[27–32] only one has found any maternal smoking to confer a statistically significant increased and separate elevated risk for both esotropia and exotropia.[27] However, in no previous study were strabismus diagnoses based on standardized comprehensive eye examinations of a population-based cohort. The likelihood of strabismus increased with the average daily number of cigarettes smoked by the pregnant mother, supporting prior reports of a dose-response effect.[27,28]

Maternal smoking also is associated with hyperopia[15] and astigmatism,[33] which are themselves risk factors for strabismus. Many previous studies investigating perinatal factors and strabismus have not adjusted for refractive error, making it difficult to determine whether the impact of smoking is direct or is indirect via refractive error. By adjusting for refractive error, smoking has been shown to be related independently to strabismus. Furthermore, excluding refractive errors from the multivariate models did not greatly alter the odds ratios for maternal smoking, suggesting that most of the effect of smoking is not mediated through its effects on refractive development. Maternal smoking during pregnancy also is known to be associated with shortened gestation and impaired fetal growth,[34,35] which are themselves risk factors for strabismus. However, the present analysis adjusted for preterm delivery and being small for gestational age, demonstrating an independent association between maternal smoking and strabismus.

The mechanism linking prenatal exposure to tobacco with strabismus or other adverse outcomes is unknown. Because the fetus is exposed directly through the placenta,[36] there could be direct toxic effects on the developing nervous system, similar to other neuro-developmental disorders known to be caused by environmental neurotoxins like tobacco.[37–40]

Hyperopia was a strong predictor of esotropia. Although esotropia is known to occur more frequently in children with hyperopia than in those without[41–43] and infants with moderate hyperopia are more likely to develop subsequent esotropia than emmetropic controls,[10,44–47] evidence-based data quantifying the risk associated with different levels of hyperopia are nonexistent. The hyperopia thresholds currently recommended for vision screening failure[48] and re-

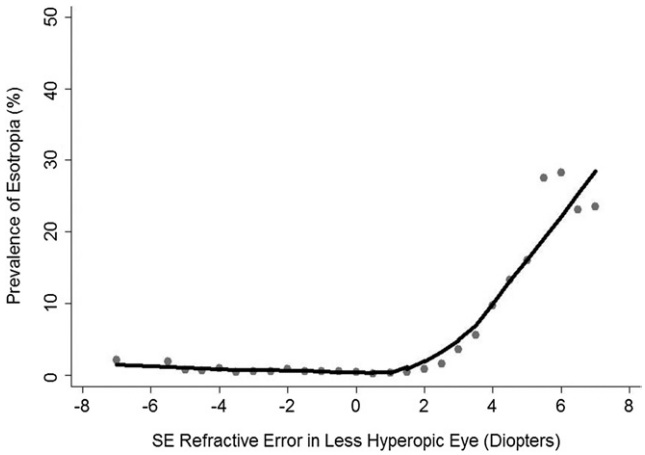

Figure 2. Locally weighted scatterplot smoothing plot illustrating the independent relationship between level of spherical equivalent (SE) refractive error and the prevalence of esotropia in 6- to 72-month-old children in the Multi-Ethnic Pediatric Eye Disease Study and the Baltimore Pediatric Eye Disease Study after controlling for other risk factors.

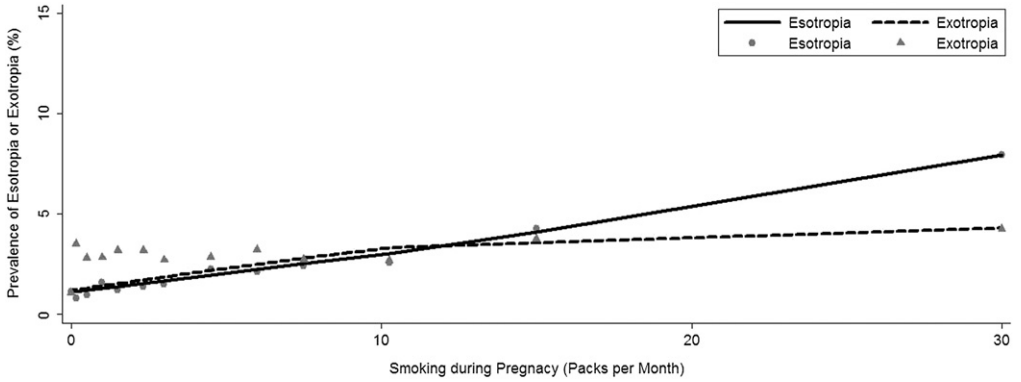

Figure 4. Locally weighted scatterplot smoothing plot illustrating the independent relationship between level of pack-months of maternal smoking during pregnancy and the prevalence of esotropia and exotropia in 6- to 72-month-old children in the Multi-Ethnic Pediatric Eye Disease Study and the Baltimore Pediatric Eye Disease Study after controlling for other risk factors.

fractive correction[49,50] are based solely on consensus. The present data show that levels of hyperopia lower than these, between 2.00 and less than 3.00 D, pose more than a 6-fold increase in esotropia risk, although the prevalence of esotropia at this level of hyperopia is modest at less than 2%. There is a marked rise in esotropia risk associated with each diopter of increasing hyperopia (Fig 2). With hyperopia of 5.00 D or more, esotropia is seen in 24% of cases, and the odds of having esotropia are 122 times greater than in children with 0 to less than 1.00 D of hyperopia. Some of the nonstrabismic children in this cross-sectional study still may be at risk of developing esotropia in the future, so the association between hyperopia and esotropia needs to be evaluated further in longitudinal studies. In addition, randomized clinical trials are needed to determine to what extent the treatment of hyperopia may prevent esotropia. In the meantime, eye care providers and parents can use the present data on the degree of increased risk associated with differing levels of hyperopia to make more informed decisions regarding the management of individual children with hyperopia (i.e., whether to monitor or provide optical correction), understanding, however, that the benefits of prophylactic spectacle treatment have yet to be proven.

Although our data indicate that esotropia risk is much greater for high levels of hyperopia than for moderate hyperopia, many fewer children are at risk from high hyperopia because it is much less prevalent.[51,52] Consequently, it is difficult to identify a single threshold level of hyperopia that is optimal as a criterion for referral of children at risk of esotropia or for consideration of prophylactic spectacle prescription. For example, as seen from the frequency distributions in Table 2, the lowest dioptric criterion that confers significant increased risk of esotropia (i.e., ≥+2.00 D), identifies nearly 18% of the present cohort as being at risk, 95% of whom do not have esotropia; however, most (74%) esotropic children would be identified. In contrast, a more conservative criterion similar to that proposed

Table 4. Independent Risk Factors* for Childhood Exotropia in 6- to 72-Month-Old Children in the Multi-Ethnic Pediatric Eye Disease Study and Baltimore Pediatric Eye Disease Study

Risk Factor	Odds Ratio (95% Confidence Interval)†	*P* Value
Maternal smoking during pregnancy	**2.88 (1.78–4.64)**	<0.0001
Gestational age <33 wks	**2.48 (1.17–5.25)**	0.018
Female sex	**1.62 (1.08–2.42)**	0.019
Astigmatism (D)‡		<0.0001
<0.50	Reference	
0.50–<1.00	0.82 (0.48–1.41)	
1.00–<1.50	1.55 (0.82–2.91)	
1.50–<2.50	**2.49 (1.30–4.79)**	
≥2.50	**5.88 (2.76–12.54)**	
J0 anisometropia (D)		0.003
<0.25	Reference	
0.25–<0.50	**2.01 (1.25–3.22)**	
≥0.50	**2.63 (1.26–5.49)**	

D = diopters.
Odds ratios in boldface are statistically significant.
*Based on multivariate stepwise logistic regression model.
†Adjusted for all factors listed in the table.
‡Level defined by the eye with the lower magnitude of astigmatism.

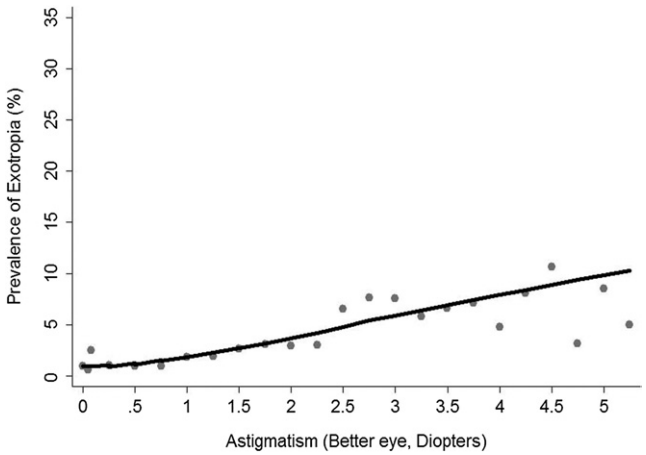

Figure 5. Locally weighted scatterplot smoothing plot illustrating the independent relationship between magnitude of astigmatism and the prevalence of exotropia in 6- to 72-month-old children in the Multi-Ethnic Pediatric Eye Disease Study and the Baltimore Pediatric Eye Disease Study after controlling for other risk factors.

by consensus guidelines (≥+4.00 D)[49,50] targets a more manageable 3% of the population, with a substantial yield (18%) of esotropia in the targeted group; however, fewer than half (40%) of all children with esotropia would be identified. Thus, these cross-sectional data do not support the existence of a hyperopia cutoff that is both sensitive and specific for associated esotropia. In any case, longitudinal data relating early refractive error to subsequent eye alignment and vision outcomes at older ages are needed to address fully questions related to screening thresholds. Although hyperopia may have some value from a screening perspective as a marker for existing strabismus—because most esotropias are of moderate size[8] and can go undetected by primary care providers—its greatest potential value in the screening setting would be as a predictor of future esotropia, amblyopia, or both, especially in light of the possible benefits of prophylactic spectacle treatment.[10]

In the case of exotropia, astigmatism showed a stronger association than did SE refractive error. Exotropia was associated with astigmatism of 1.50 D or more in the less astigmatic eye. There are few studies with which this risk association can be compared. Although astigmatism previously has been noted to be associated with strabismus in general, a separate analysis of esotropia and exotropia were not reported.[53,54]

An association between esotropia and SE anisometropia also was detected, as well as an association between exotropia and anisoastigmatism in the J0 component, after adjusting for other risk factors. Previous studies reported associations between anisometropia and strabismus, but did not analyze esotropia and exotropia separately.[53–55] Data from a hyperopia-enriched clinic population indicated that coexisting anisometropia increased the risk of esotropia in the presence of hyperopia.[56,57] Although a significant statistical interaction between hyperopia and anisometropia in the present analysis of esotropia was tested for, none was detected. Associations between anisometropia and strabismus are highly plausible from a clinical perspective. Anisometropia has been shown to reduce binocularity in patients without strabismus,[58,59] and clinicians view uncorrected anisometropia as a sensory fusion obstacle to normal binocular vision.

Gestational age less than 33 weeks was associated independently with increased risk of both esotropia and exotropia. Several prior studies reported shortened gestation to be associated with childhood esotropia, exotropia, or strabismus in general.[55,60–65] The present findings cannot be compared directly with these because of differing definitions of prematurity, use of clinical samples as opposed to the population-based cohort, data analyses not adjusted for other potentially confounding risk factors, and nonuniform determination of and definitions of strabismus.

Older preschool age, specifically 48 to 72 months, conferred an 8- to 9-fold increased risk of esotropia. There was no age association with exotropia. The authors are not aware of any study showing an independent risk association between older preschool age and esotropia after adjusting for other risk factors. However, longitudinal studies have shown that strabismus is rare in the first year of life.[10,44,66] Furthermore, esotropia is more prevalent in 36- to 72-month-old MEPEDS participants than in those 6 to 35 months of age,[8] and the BPEDS similarly reported a very low prevalence of strabismus among 6- to 11-month-old children.[9] These findings are not likely to be an artifact of failure to detect strabismus in younger children, because esotropia prevalence increased with age even after excluding small-angle deviations.[8] The present analysis adjusting for all other risk factors provides even more robust evidence for a strong relationship between age and esotropia, probably because the most prevalent form of esotropia, accommodative esotropia,[11,12] occurs more commonly when hyperopic children are older and accommodating more consistently.

We found that being female was associated independently with exotropia. Although a predominance of girls has been reported among incident cases of intermittent exotropia in children younger than 19 years in a semiurban white population,[67] to our knowledge, the present study is the first population-based report that has controlled for confounding variables to find this association.

There was an independent association between positive family history of strabismus and exotropia. These results are consistent with long-held clinical observations[68–70] and data from a large cohort study[71] that there is a significant familial component in the cause of strabismus. A wide range of confounding factors were adjusted for in the present study, in particular refractive error, thus suggesting that the heritability of exotropia is not merely the result of the heritability of refractive error.[72]

As with many epidemiologic investigations, our study has a number of potential limitations. Because of missing data, 1479 participants were excluded from the analysis, but significant differences in characteristics of those included versus those excluded in the analysis were not found, with the exception that among excluded children, female sex was not associated with exotropia. However, when the excluded and included were collapsed into 1 sample, the univariate association between sex and exotropia persisted, although it was diminished. Parental report was relied on for determination of demographic and behavioral factors. Mothers of children without vision disorders selectively may have underreported smoking and alcohol use during pregnancy. It is unlikely that our findings were impacted substantially by recall bias because these questions were just 2 of many that were asked during a prolonged interview, which preceded the conclusion of the clinical examination with its attendant discussion of ocular findings, and self reports have been shown to be a valid indicator of actual smoking levels.[73] A finite number of potential risk factors necessarily were explored. It is possible that other unknown or unexplored factors known to affect development, such as maternal diet during pregnancy and environmental toxins, including maternal second-hand smoke during pregnancy, also may contribute to strabismus. Prior successful treatment of strabismus may mask or underestimate risk associations; however, a minority of the strabismic participants had received prior treatment. Because of the cross-sectional design, confirmation of refractive error and alignment was available only for the time of clinical examination. Thus, for older children, it is possible that their refractive error may have been different at an earlier age; and likewise, there may be younger children at risk for strabismus who have yet to develop strabis-

mus, which could lead to underestimation of the strength of associations with refractive error. The cross-sectional design also precludes determination of the temporal relationship between the identified risk factors and strabismus. Thus, longitudinal study is needed to confirm the present cross-sectional findings.

The main strengths of this study include the large, ethnically diverse cohort of children from 2 distinct geographical areas in the United States and the population-based design. Compared with clinic-based samples that overrepresent severe disease, this study is more likely to be generalizable to the population as a whole, and risk associations are less likely to be spurious. A particular strength is that all children received comprehensive eye examinations by study-certified eye care providers who followed a standardized protocol, determining refractive error by cycloplegic refraction and strabismus by cover testing; thus, misclassifications should be rare. By using multivariate analysis, the independent impact of a broad range of potential risk factors for strabismus was evaluated without confounding from coexisting risk factors.

In conclusion, this population-based study of childhood strabismus established a strong dose-dependent link between refractive errors and strabismus and confirmed the role of other risk factors, such as premature birth and gestational exposure to maternal smoking. Because refractive errors may be targeted for early intervention, the data herein provide valuable information to help guide providers and patient families in making informed decisions regarding management of early refractive error. However, longitudinal study is needed both to confirm the predictive value of uncorrected refractive error and to evaluate the potential impact of early treatment.

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