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Prevalence, Characteristics, and Risk Factors of Moderate/High Hyperopia among Multiethnic Children 6 to 72 Months Old – A Pooled Analysis of Individual Participant Data

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Abstract

Purpose: To describe the prevalence, ocular characteristics, and associated risk factors of moderate/high hyperopia in early childhood.

Design: Pooled analysis of individual participant data from population-based studies.

Subjects: 6- to 72-month-old, multiethnic children who participated in four population-based studies of pediatric eye diseases.

Methods: The pooled studies conducted comparable parental interviews and ocular examinations including cycloplegic autorefraction. Presence of hyperopia was defined based on cycloplegic refractive error in the worse eye. Multivariable analyses were performed to evaluate the association of potential risk factors with hyperopia risk.

Main Outcome Measures: Prevalence and odds ratios of moderate/high hyperopia (≥4.0 D).

Results—Cycloplegic refraction was completed in 15,051 children 6 to 72 months of age. Among these children, the overall prevalence of moderate/high hyperopia (≥4.0 D) in the worse eye was 3.2% (95% confidence interval, 2.9%-3.5%), accounting for 15.6% of all hyperopia (≥2.0 D). Among children with moderate/high hyperopia, 64.4% had both eyes affected, 28.9% had spherical anisometropia of 1.0 D or greater, and 19.5% had astigmatism of 1.5 D or greater. Among 36- to 72-month-old children with moderate/high hyperopia, 17.6% wore glasses. Prevalence of moderate/high hyperopia was slightly less in 12- to 23-month-old children and was relatively stable in children aged 24 months and older. Non-Hispanic and Hispanic white race/ethnicity, family history of strabismus, maternal smoking during pregnancy, and being a participant in the U.S. studies were associated with a higher risk of moderate/high hyperopia ($P<0.05$).

Conclusions: By assembling similarly-designed studies, our consortium provides robust estimates of the prevalence of moderate/high hyperopia in the general population and shows that in 6- to 72-month-old children moderate/high hyperopia is not uncommon and its prevalence does not decrease with age. Risk factors for moderate/high hyperopia differ from those for low/moderate hyperopia (2.0 D to <4.0 D) in preschool children, with family history of strabismus and maternal smoking during pregnancy more strongly associated with moderate/high hyperopia than low/moderate hyperopia.

INTRODUCTION

Hyperopia is a common refractive error in young children and its prevalence varies by race/ethnicity[1] and geographic region.[2] Hyperopia, especially moderate/high hyperopia, has been adversely associated with children's vision development, various visual functions, and academic performance.[3–6] Children 30 to 72 months of age with ≥4.0 D of hyperopia were found to have 10.8 times the risk of decreased bilateral visual acuity compared to emmetropic children.[3] The presence of esotropia was associated with hyperopia in a severity-dependent manner, with relative risks increasing from 6.4 for 2.0 D to <3.0 D of hyperopia up to 59.8 for ≥4.0 D of hyperopia in children 6 to 72 months of age.[4] The Vision in Preschoolers-Hyperopia in Preschoolers (VIP-HIP) Study[5] found that the proportion of children with reduced visual functions (visual acuity, near stereoacuity, and/or

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accommodative response) increased from 17% in emmetropic children to 82% in children with uncorrected hyperopia of ≥4.0 D to ≤6.0 D. They also found that ≥4.0 D of uncorrected hyperopia was associated with worse performance on early literacy tests in 4- and 5-year-old children.[6]

Early detection and treatment of hyperopia may help reduce these adverse impacts of hyperopia on young children. Visual-motor function delays[7] and poor literacy[8, 9] in children with uncorrected hyperopia have been shown to improve with spectacle correction in some studies. The risk of developing strabismus and amblyopia in 9-month-old children with hyperopia was also reduced by wearing a partial hyperopic spectacle correction without affecting emmetropization in one study.[10] Although there is no consensus regarding the threshold for prescribing spectacles[11, 12] and the effect of spectacle correction on the risk of developing amblyopia and strabismus[13–16] for young children with hyperopia, it is generally agreed that hyperopia of 4.0 D or greater warrants consideration of spectacle correction or at least close monitoring.[17] With automated methods of refraction increasingly available for screening preschool children, it is important to identify populations at risk for moderate/high hyperopia that may benefit from early detection and intervention. Major risk factors for preschool hyperopia of 2.0 D or greater have been examined previously[18] and factors such as white race, maternal smoking during pregnancy, and having health insurance were found to be associated with a higher risk of hyperopia. However, it remains unclear whether the same risk factors are also important for moderate/high hyperopia, and whether hereditary factors play a significant role in moderate/high hyperopia,[19] in part because individual studies generally do not have adequate numbers of moderate/high hyperopia cases for statistical analyses.

To fill these gaps, we pooled individual participant data from four population-based studies,[20–23] to generate a broader and more precise estimate of the prevalence and characteristics of moderate/high hyperopia (defined as 4.0D or greater) in 6- to 72-month-old children and identify demographic, behavioral, and clinical risk factors that may be associated with a higher risk of moderate/high hyperopia. We also conducted a comparable analysis for low/moderate hyperopia (2.0 D to <4.0 D).

MATERIALS AND METHODS

Study Cohort

Systematic review of the literature identified four studies that met the following inclusion criteria: (1) population-based study, (2) conducted among pre-school age children, (3) performed standardized, comprehensive ocular examinations on all eligible participants with outcomes assessed in both eyes, and (4) assessed potential risk factors in sufficient detail. These four studies formed the Population-based Pediatric Eye Disease Study Consortium (POPEYE consortium): the Multi-Ethnic Pediatric Eye Disease Study (MEPEDS) conducted in Los Angeles, California, United States;[20] the Baltimore Pediatric Eye Disease Study (BPEDS) conducted in Baltimore, Maryland, United States;[21] the Strabismus, Amblyopia and Refractive Error in Singaporean Children Study (STARS) conducted in Singapore;[22] and the Sydney Pediatric Eye Disease Study (SPEDS) conducted in Sydney, Australia.[23] The details of participant recruitment in each study have been reported elsewhere.[20–23] Written

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informed consent was obtained from a parent or guardian (hereafter referred to as parent) of each participating child in the original studies.

De-identified individual participant data were pooled from these four studies and compiled into a central database. Study protocols, questionnaires, and data dictionaries were obtained from each study to facilitate data harmonization. These studies shared core eye examination and clinical interview protocols for all primary outcome measures at the design stage, and similar questionnaires with identical core questions were administered. Data from each study were checked for consistency across studies before pooling. Meetings were organized between individual study investigators to adjudicate differences in phenotype classifications and variable definitions. The protocols for this investigation were reviewed and approved by the Institutional Review Board /Ethics Committee at the Keck School of Medicine of the University of Southern California and adhered to the tenets of the Declaration of Helsinki.

Ocular Examination and Interview

Details of ocular examination and interviews conducted in the individual studies have been reported previously.[18, 20–23] Briefly, for all studies, a comprehensive eye examination was performed by optometrists or ophthalmologists, trained and certified using standardized protocols. The eye examination included assessments of visual acuity, stereoacuity, ocular alignment and ocular motility testing, ocular health, ocular biometry measurement, and cycloplegic refraction. Details of cycloplegic refraction are summarized in the Supplemental Method. For children whose parents refused cycloplegic eye drops, noncycloplegic refraction measurements were obtained. However, for the current analyses, only participants that received at least two drops of cyclopentolate were included due to concerns of variable refraction measurements resulting from incomplete cycloplegia.[24] After cycloplegia, axial length was measured using a noncontact partial coherence interferometer (IOLMaster) in all four studies and the average of 3 to 5 repeated readings was used for analyses. Keratometry was conducted using a handheld Retinomax to measure corneal power and corneal curvature.

On the day of the clinical examination, participating child’s parent(s) were interviewed by trained interviewers using standardized questionnaires to collect data on demographic characteristics, family history of eye diseases, and ocular and medical history of the participants. Supplemental questions that were not included for all four studies are not considered in this report.

Statistical Analysis

The analysis cohort consisted of all children in whom reliable cycloplegic refraction could be obtained. Children with reported diagnosis of Down syndrome or cerebral palsy were excluded from analyses (Supplemental Figure 1). Race/ethnicity as identified by parental report was grouped as Hispanic white (racially white Americans with Hispanic descent, i.e., Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin), non-Hispanic white (European Caucasians and Australians having origins in Europe or Middle East, white Americans that are not of Hispanic descent), African Americans, Asians (Americans having origins from the Far East, Southeast Asia, or the Indian

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subcontinent, Singapore Chinese, Australian with East and South Asian ethnicity). In terms of Asian participant's ethnicity, 60% of Asians in SPEDS (based on parental report), 59% of Asians in MEPEDS (based on the reported language spoken at home), and all STARS participants (Chinese only) were East Asian. Prevalence of any hyperopia or moderate/high hyperopia was not significantly different between East Asians and other Asians in MEPEDS and SPEDS (Ps>0.05). Children from other racial/ethnic backgrounds were excluded due to their small sample size. Characteristics of participants included in the analysis cohort were compared to those of excluded children using chi-square test, t-test, and analysis of variance where appropriate.

Spherical equivalent (SE) refractive error was calculated as the sphere power plus ½ of the cylinder power. Any hyperopia was defined as SE hyperopia ≥2.0 D, low/moderate hyperopia as SE hyperopia of 2.0D to <4.0D, and moderate/high hyperopia as SE hyperopia ≥4.0 D in the worse eye for the primary analysis. SE hyperopia <2.0D was considered as non-significant hyperopia. Emmetropia was defined as SE refractive error between −0.5 D and +0.5 D, non-inclusive, in both eyes. The worse eye was defined as the eye with the greater hyperopic SE refractive error. If only one eye had refractive error data, that eye was considered to be the worse eye. The 95% confidence interval (CI) for prevalence was estimated using the exact method. The contribution to hyperopic refractive error of axial length, corneal curvature radius (CCR), and the ratio of axial length-to-CCR was evaluated by assessing the magnitude of the coefficient of determination (R^2) in multivariable linear regression of refractive error among 36- to 72-month-old children without myopia (SE > −0.5 D). R^2 measures the proportion of the variance in the refractive error that can be explained by a given biometric variable. Logistic regression was used to assess whether glasses wear was associated with the following parameters: study, child's age, sex, race/ethnicity, education level of primary caregiver, low income, gestational age, and birth weight in children with hyperopia.

Sociodemographic, behavioral, and clinical risk factors that have been previously suspected or associated with refractive error in young children[18, 25–28] and were collected in the four participating studies were evaluated for their association with hyperopia. Sociodemographic factors evaluated were age group; sex; racial/ethnic group (Hispanic white, non-Hispanic white, African American, and Asian); low income (yes, no); and education level (< high school graduate, high school graduate, college/university graduate or more) of the primary caregiver (biological mothers accounted for 83% and 97% of primary caregivers in MEPEDS and BPEDS, respectively) or the biological mother (SPEDS and STARS). Behavioral and clinical risk factors evaluated were maternal smoking during pregnancy (yes or no); maternal alcohol consumption during pregnancy (yes or no); gestational diabetes (yes or no); preeclampsia (yes or no); maternal anemia during pregnancy (yes or no); maternal hypertension (yes or no) during pregnancy; other pregnancy complications (yes or no); maternal age at childbirth (<35 years; 35-<40 years; and 40+ years); gestational age (≤36 weeks; 37-<42 weeks; ≥42 weeks); birth weight (<2.5kg; 2.5-4.2 kg; and >4.2 kg); breastfeeding (yes or no); family history of strabismus (yes or no) or amblyopia (yes or no) in first-degree relatives.

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To identify independent factors associated with hyperopia risk, multivariable logistic regression analyses with forward stepwise selection were performed with a $P \leq 0.20$ criterion for entry into the model and P ≤0.05 for retention in the model. Model selection was performed with any hyperopia (≥2.0 D) as the outcome. Model selection with moderate/high hyperopia as the outcome was also performed and no additional risk factors were identified. For risk factors with missing data, a missing-value indicator[29] was created for each risk factor to keep the most participants' data in the analyses. Risk factors identified through this method were further validated through complete-case analyses and analyses with imputed data. For the variables selected in the final model, there were no material differences in the analysis results of the full data using missing indicator method, those of the complete data, and those of the imputed data; therefore, results from analyses with complete data were reported. Odds ratios with 95% CI's were reported for the risk factors included in the final model. Between-study heterogeneity in the association between independent risk factors and hyperopia was tested by including proper cross-product terms in the regression models. When significant heterogeneity was present, subgroup analysis stratified by study was performed for generating study-specific estimates and influence of data from an individual study was assessed through leave-one-out-analyses by iteratively removing one study at a time.

Quantile regression was used to explore the impact of potential risk factors at different levels of hyperopia using cutoff points determined by internal percentile ranks, rather than prespecified thresholds (such as the 2.0 D or 4.0 D thresholds used for logistic regression) or the mean value of refractive error (as in ordinary linear regression). Multivariable quantile regression, which estimates the conditional median or other quantiles of an outcome variable with respect to covariates, was used to evaluate the effect of identified risk factors on 0.05 to 0.95 percentile (by 0.05 interval) of refractive error after controlling for other covariates. The 95% CIs were estimated using the sparsity function.

All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC) with a significance level set at P ≤0.05. All reported P values are two-sided.

RESULTS

In total, the consortium included 17,214 children with ocular examination data from four studies, representing 74% of the eligible participants (Supplemental Figure 1). There were 456 children from racial/ethnic groups (e.g., Pacific Islander) with few participants, 43 children with Down's syndrome or cerebral palsy, and 371 children who were younger than 6 months or older than 72 months at the time of examination; these children were excluded from subsequent analyses. Among the remaining 16,344 participants, 15,051 (92%) had undergone cycloplegic refraction of at least one eye measured after two or more drops of cyclopentolate. Refraction was measured using the Retinomax autorefractor, retinoscopy, or the Canon autorefractor in 74%, 16%, and 10% of children, respectively. Cycloplegic refraction was more commonly completed in older children (95.1% in 60- to 72-month-olds vs. 89.5% in 6- to 11-month-olds), Hispanic whites (98.4%) and African Americans (95.2%) versus non-Hispanic whites (89.1%) and Asians (87.8%), and BPEDS (94.1%) and MEPEDS (93.7%) versus SPEDS (89.2%) and STARS (87.7%) (P < 0.05 for all).

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Completion of cycloplegic refraction did not vary by sex or ocular history (e.g., amblyopia, strabismus, myopia, wearing glasses or contact lenses). The demographic characteristics of the participants with cycloplegic refraction data are shown in Table 1. Each of the four racial/ethnic groups had more than 3,000 participants; 48% were female and 8% were less than 1 year of age with nearly equal proportions of participants in the remaining age groups.

Prevalence of low/moderate and moderate/high hyperopia by demographic factors

Table 2 presents the prevalence of any (≥2.0 D), low/moderate (2.0 D to <4.0 D), and moderate/high (≥4.0 D) hyperopia for the worse eye, stratified by race/ethnicity, sex, and age group. Among these 6- to 72-month-old children, the overall prevalence of moderate/high hyperopia in the worse eye was 3.2%, accounting for 15.6% of all hyperopic children. Similar to low/moderate hyperopia, there was a significant race/ethnicity difference in the prevalence of moderate/high hyperopia (P<0.001), with the highest prevalence observed in Hispanic whites and non-Hispanic whites and the lowest prevalence in Asians. This race/ethnicity difference was consistently observed in all four studies (Supplemental Figure 2) and remained after adjusting for age (data not shown). There was a higher prevalence of low/moderate hyperopia in girls versus in boys (P<0.001), but similar sex-difference was not observed for moderate/high hyperopia (P=0.96). This was found in all four studies for all race/ethnicity groups except Hispanic whites (P for se-difference in low/moderate hyperopia=0.83). While the prevalence of low/moderate hyperopia was greatest in 6- to 11-month-old children and then stabilized after 24 months, the prevalence of moderate/high hyperopia was the same or greater for all age groups older than 6-11 months, with the exception of 12- to 23-month-old children. The associations with race/ethnicity, sex, and age group showed the same patterns in our multivariate analyses (see below and Table 4).

Prevalence data for hyperopia in the right eye and in the better eye are available in Supplemental Table 1.

We examined the proportion of 36- to 72-month-old children who were reported to wear glasses (Table 3). Glasses wear was reported for 17.6% of children with moderate/high hyperopia in the worse eye and 20.5% (data not shown in tables) of children with moderate/high hyperopia in both eyes. Glasses wear was less common in African American children with moderate/high hyperopia (6.6%) than children from other racial/ethnic groups with moderate/high hyperopia (28.4%, 23.4%, and 15.2% in non-Hispanic whites, Asians, and Hispanic whites, respectively; P for race=0.039) and less common in 36- to 47-month-olds (11.7%) than in 60- to 72-month-olds (24.3%) (P for age trend=0.048), but was not significantly different by study, household income level, education level of the primary caregiver, and other factors evaluated (data not shown in tables).

Ocular characteristics of low/moderate and moderate/high hyperopia Of the children with moderate/high hyperopia, 64% (310/481) had moderate/high hyperopia in both eyes, and 36% had moderate/high hyperopia in one eye only (Table 3). Both spherical anisometropia ≥1.0 D and astigmatism ≥1.5 D were much more common in children with moderate/high hyperopia (28.9% and 19.5%, respectively) than children with low/moderate hyperopia (6.4% and 10.2%) and emmetropia/no significant hyperopia (0.9% and 5.2%). Similar proportions were observed in the 36- to 72-month-old subset of older children.

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There were no age differences in the prevalence of astigmatism and anisometropia among children with moderate/high hyperopia (P for age trend= 0.18 and 0.87, respectively).

We compared axial length, corneal power, and CCR across different levels of hyperopia severity in 36- to 72-month-old children, from whom reliable biometry measurements were obtained (Table 3). Shorter axial length, lower corneal power, greater CCR, and smaller axial length-to-CCR ratio were observed for hyperopia in a severity-dependent manner (P<0.001 for all). These differences remained even after adjustment for age, sex, race/ethnicity, and study (data not shown). The proportion of variance in hyperopic refractive error that can be attributed (R^2) to axial length alone, CCR alone, or axial length/CCR ratio was estimated to be 0.251, 0.002, and 0.419, respectively.

Risk factors associated with low/moderate and moderate/high hyperopia

Race/ethnicity, sex, age, study, level of education of primary caregiver, maternal smoking during pregnancy, and family history of strabismus were identified to be associated with the prevalence of any hyperopia. Family history of amblyopia was positively associated with any hyperopia and maternal hypertension during pregnancy was negatively associated with any hyperopia in the analysis of full data using missing-indicator method. However, these two factors did not remain associated with any hyperopia in the analyses with imputed data for missing values (P= 0.078 and 0.055, respectively) and were not associated with moderate/high hyperopia, and therefore were removed from the final model. Estimates for other identified risk factors were not materially changed with and without these two factors.

The results of the multivariable analysis of the associations between the identified risk factors and having either low/moderate or moderate/high levels of hyperopia are shown in Table 4. Results were similar with additional adjustment for astigmatism (data not shown). The patterns of association of low/moderate and moderate/high hyperopia with race/ethnicity, sex, and age were discussed above, and remained similar after adjustment for other covariates. Family history of strabismus conferred a 54% higher risk for moderate/high hyperopia but was not associated with low/moderate hyperopia. Having a less educated primary caregiver was also associated with high prevalence of any hyperopia; however, the association was significant only for low/moderate hyperopia. Maternal smoking during pregnancy was associated with a 28% higher risk of low/moderate hyperopia and 64% higher risk of moderate/high hyperopia. The impact of intensity, period, duration, and cigarette-months of smoking were also evaluated (Table 4). Even a modest amount (<5 cigarettes/day) of smoking was associated with a higher risk for moderate/high hyperopia. While a short duration of smoking conferred a higher risk only for low/moderate hyperopia, longer duration of smoking, especially smoking in the third trimester, was associated with a much higher risk of moderate/high hyperopia.

Significant differences in low/moderate and moderate/high hyperopia were also observed between studies, after adjusting for race/ethnicity and other risk factors that might vary by study. The highest risk of hyperopia was associated with the MEPEDS and the BPEDS in the U.S., and the lowest with the STARS in Singapore (Table 4). We also evaluated between-study heterogeneity in the association between independent risk factors and hyperopia. No significant heterogeneity was found except for the associations of age and education level of

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primary caregiver with low/moderate hyperopia (P's for heterogeneity=0.002 and 0.003, respectively; Supplemental Table 2).

To further explore the effect of the identified risk factors at different levels of hyperopia using cutoff points determined by internal percentile ranks, multivariable quantile regression was performed for refractive error in the worse eye. Over the entire cohort, refractive error was distributed such that −0.625 D, −0.125 D, +1.125 D, +2.625 D and +3.45 D represented the 5th, 10th, 50th, 90th, and 95th percentile values, respectively. However, the percentile values for levels of refractive error varied with age and race/ethnicity (Supplemental Figure 3). After controlling for other factors associated with hyperopia, age was associated with refractive error in a complex manner (Figure 1). Overall, there was a hyperopic shift with age in the refractive error levels defining the lower quantiles (more myopic/less hyperopic end) (Figure 1F). Refractive errors associated with non-Asian ethnicity, U.S. studies, maternal smoking during pregnancy, and family history of strabismus were consistently more hyperopic at the upper quantiles (hyperopic end) of the distribution, and their effect sizes were generally greater at more extreme quantiles (Supplemental Figure 4).

The impact of risk factors for hyperopia on axial length, CCR, and axial length/CCR ratio are presented in Supplemental Table 3. Maternal smoking during pregnancy was associated with shorter axial length and smaller CCR.

DISCUSSION

Using cycloplegic refraction data from more than 15,000 participants of four population-based studies, we present much needed data characterizing the prevalence, ocular characteristics, and associated risk factors for moderate/high hyperopia (≥4.0 D) in children 6 to 72 months of age. We found moderate/high hyperopia was not uncommon in young children and its prevalence did not decrease with age. A family history of strabismus and maternal smoking during pregnancy, especially maternal smoking that persisted into the third trimester, were more strongly associated with moderate/high hyperopia than low/moderate hyperopia in this combined cohort. Non-Hispanic and Hispanic white race/ethnicity were associated with a higher risk of moderate/high hyperopia even after accounting for other factors.

Young children with moderate/high hyperopia are at much higher risk for strabismus,[30] reduced visual acuity,[3] near stereoacuity, and accommodative response,[5] and deficits in early literacy; [6] thus, better surveillance for early identification and close monitoring by eye care professionals are needed for these children. Additionally, having anisometropia or astigmatism in addition to hyperopia increases the risk of strabismus or amblyopia further; [3, 23, 30] we found that 44.3% of children with moderate/high hyperopia had either anisometropia of 1.0 D or greater or astigmatism of 1.5 D or greater. Similar observations were also reported by the VIP Study.[31] Despite the high risk for strabismus and amblyopia in these children, only a small proportion (17.6%) of 36- to 72-month-old children with moderate/high hyperopia wore glasses. Furthermore, African American children with moderate/high hyperopia were less likely to be wearing glasses than children from other racial/ethnic groups, even after adjustment for household income and education level of the

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primary caregiver. This low proportion of optical correction in children with moderate/high hyperopia, even in those aged 36- to 72-months, could be due to the ongoing debate on the need for optical correction for these children among eye care providers, underestimation of the importance of optical correction by parents, and/or underdiagnosis of hyperopia. Data from MEPEDS showed that few preschool children had ever previously had a dilated eye examination, ranging from 2.8% among 6- to 11-month-old children to 11.6% among 61- to 72-month-old children.[32] A lack of surveillance and treatment of moderate/high hyperopia in preschool children can result in irreversible vision impairment, as preschool age remains a critical period for the effective treatment of strabismus and amblyopia.

Hyperopia can result from variations in multiple ocular components (short axial length, flat cornea, low lens power, or a combination of these factors) which may be influenced by different genetic/environmental factors. We found that in 36- to 72-month-old children, from whom biometry data can be more reliably measured, an abnormally low axial length-to-CCR ratio is a more important contributor to hyperopia (explaining ~42% of the variation in hyperopic refractive error) than a short axial length or a greater CCR alone. Maternal smoking during pregnancy and a family history of strabismus both seem to contribute to higher hyperopia risk through associated shorter axial length. Racial/ethnic differences in hyperopia prevalence, on the other hand, can result from variations in either CCR or axial length (see below). Future studies with data on other ocular components (e.g., vitreous chamber depth, lens thickness, anterior chamber depth) are needed to further explore ocular determinants of preschool hyperopia.

Prevalence of both moderate/high hyperopia (≥4.0 D) and low/moderate hyperopia (2.0 D to <4.0 D) vary by race/ethnicity. Overall, non-Hispanic and Hispanic white children have a higher risk of hyperopia than African American and Asian children. This racial/ethnic difference was consistently seen across studies and remained after controlling for other potential risk factors for hyperopia, suggesting that genetic differences or racial/ethnic differences in other uncontrolled environmental or behavioral factors may play a role. The higher risk of hyperopia in non-Hispanic whites may be attributable in part to shorter axial length, whereas the higher prevalence of hyperopia in Hispanic whites may be attributable more to a disproportionately flatter corneal curvature. The observation of Hispanic whites having greater CCR and less corneal power and Asians and Hispanic whites having longer axial lengths is consistent with previous studies.[33, 34] The observation of Asian children having longer axial lengths than other racial/ethnic groups even in preschool age, suggests that Asians are predisposed to myopia even before a significant school-age myopic shift occurs.

Even though longitudinal data were not available for us to investigate how an individual child’s refractive error develops in preschool age, our cross-sectional comparison of refractive error distributions across different age groups suggested the following age-related changes. First, children with different initial levels of refractive error may undergo different developmental changes in refraction from 6 months to 72 months of age. While myopic eyes may go through a progressive hyperopic shift toward emmetropia over the first few years of life, hyperopic eyes may undergo a myopic shift mostly in the first year of life. Second, it is likely that refractive error does not change significantly between 3 and 5 years of age.

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Consequently, as our prevalence estimates indicate, the prevalence of moderate/high hyperopia remains relatively stable or even increases slightly in children aged 2 years and older. These findings suggest that screening for hyperopia may reasonably be initiated as early as 2 years of age. Nonetheless, prospective studies that monitor longitudinal changes in preschool refraction are needed to confirm these observations.

In addition to confirming previous reports of an association between maternal smoking during pregnancy and a higher risk of hyperopia[1] and greater amounts of hyperopia,[35] we found that even a modest level (<5 cigarettes/day) of maternal smoking during pregnancy conferred a higher risk for moderate/high hyperopia, and third trimester smoking may be a more important determinant of moderate/high hyperopia risk than early-pregnancy smoking. Other studies have reported that late pregnancy was more sensitive to the adverse effects of smoking on fetal growth[36] and the development of oculomotor control.[37] The effect of maternal smoking during pregnancy on hyperopia risk does not seem to be mediated by a higher risk of preterm birth and/or low birth weight, neither of which was associated with hyperopia in this study. Biometric analysis revealed that maternal smoking during pregnancy was associated with reduced axial length and CCR. This is consistent with findings that nicotine may inhibit eye growth in animal models[38] and that maternal smoking may be associated with an increased risk of anophthalmia and microphthalmia.[39] Unfortunately, despite many tobacco control efforts, smoking during pregnancy is still prevalent in many countries.[40] With the rapid increase of e-cigarette use in young adults and the perception of relative safety, e-cigarette use during pregnancy and therefore fetal exposure to nicotine is expected to increase.[41] It remains unclear how maternal exposure to e-cigarettes will impact the vision of the developing fetus.

The finding of an association between family history of strabismus and a higher risk of moderate/high hyperopia was not surprising. It is known that hyperopia, especially moderate/high hyperopia, is a strong risk factor for esotropia.[30] Among MEPEDS and BPEDS participants with esotropia, 73.5% (75 out of 102) had hyperopia of 2.0 D or greater and 40.2% (41 out of 102) had hyperopia of 4.0 D or greater. In the present analysis, family history of strabismus is likely a surrogate marker for family history of hyperopia, which was not directly assessed. Unfortunately, our knowledge of genetic variations contributing to strabismus and hyperopia remain limited and genetic susceptibility loci shared by the two traits have not been identified to date.[42] Our data also support a higher risk of hyperopia for females, possibly due to a smaller AL/CCR ratio. However, the average sex-difference in hyperopia is small, with females being approximately 0.1 D more hyperopic than males, and there is no significant difference in the risk of moderate/high hyperopia.

This study has unique strengths, including a very large sample size comprised of four population-based studies from three different countries that performed similar standardized ocular examinations and parental interviews allowing for comparisons by race/ethnicity. Because of these advantages, prevalence estimates from this study are less likely to be impacted by selection bias than those from clinic-based studies and may be more generalizable to other similar populations. Despite methodological similarities, significant between-study differences were found, both with regard to the adjusted risk of hyperopia, and (in the case of low/moderate hyperopia) its associations with age and education of

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primary caregiver. These differences may result from demographic or environmental differences not captured in our analyses, or from methodological differences. The differences in the cycloplegia protocol and refraction method across studies may have contributed in part to the between-study differences in the magnitude of age effect. In addition, heterogeneity within a given racial/ethnic group may have contributed to between-study variation persisting after adjustment for race/ethnicity. For example, there may be additional genetic differences between non-Hispanic whites residing in different geographical locations. Better assessment of ethnicity or genetic ancestry are needed. Furthermore, having a less-educated primary caregiver might in fact be an indirect surrogate for other factors such as maternal substance misuse in pregnancy,[43] and as such may more closely reflect increased risk in some countries more than in others. Given these considerations, there is a theoretical concern that because almost all Hispanic white participants were recruited through MEPEDS and all African Americans were recruited through MEPEDS and BPEDS, our observed racial/ethnic differences in hyperopia prevalence may be confounded by methodological, demographic, or environmental differences between studies. However, the confounding is not likely to be substantial, as the racial/ethnic differences in hyperopia risk remained after adjusting for study and are furthermore consistent with those reported by MEPEDS,[44] in which four different ethnic groups were recruited from the same geographical location (Los Angeles, CA) and evaluated using identical methods.

This large pooled study has a number of other limitations as well. Even though refractive error was measured by cycloplegic autorefraction for most children, retinoscopy was used for children for whom an autorefraction measurement was unsuccessful in MEPEDS and BPEDS or for the youngest children in SPEDS and STARS. The difference in the choice of refraction method between participants is unlikely to affect our results substantially, as no clinically significant differences in refraction results were found among different cycloplegic autorefraction methods and cycloplegic retinoscopy.[24] Our threshold definitions of low/moderate hyperopia as 2.0 D to < 4.0 D and moderate/high hyperopia as ≥ 4.0 D are of necessity somewhat arbitrary and could have led to the misclassification of some participants. However, the associations that we observed between various risk factors and hyperopia are robust, as shown by our quantile regression analyses, which revealed consistent patterns at the hyperopic end of the refractive error distribution. Also, participants in this combined cohort were all recruited from urban areas and therefore prevalence estimates from this study may be not applicable to children from rural areas, as rural residency has been associated with a higher prevalence of hyperopia in some studies.[26]

In conclusion, using a large set of pooled individual participant data, we have provided prevalence estimates and described ocular characteristics of moderate/high hyperopia, and explored various demographic, behavioral, and clinical associations with moderate/high hyperopia (≥4.0 D) and low/moderate hyperopia (2.0 D to <4.0 D). We found that moderate/high hyperopia was not uncommon in 6- to 72-month-old children and its prevalence does not decrease with age. and a large proportion of these young children with moderate/high hyperopia had either anisometropia or astigmatism. We also characterized the association of maternal smoking during pregnancy with hyperopia risk and found that maternal smoking persisting into the third trimester was associated with a much higher risk of moderate/high

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hyperopia. Further studies are needed to clarify the longitudinal patterns of refractive change in early childhood and biological mechanisms underlying the association between gestational exposure to tobacco smoke and hyperopia, and to characterize other social/environmental factors that may account for variations in adjusted risk for hyperopia at different studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Précis

Pooled analyses of population-based studies found that hyperopia ≥4.0D is not uncommon and often accompanied by anisometropia or astigmatism in 6- to 72-month-old children and has distinct risk factors.

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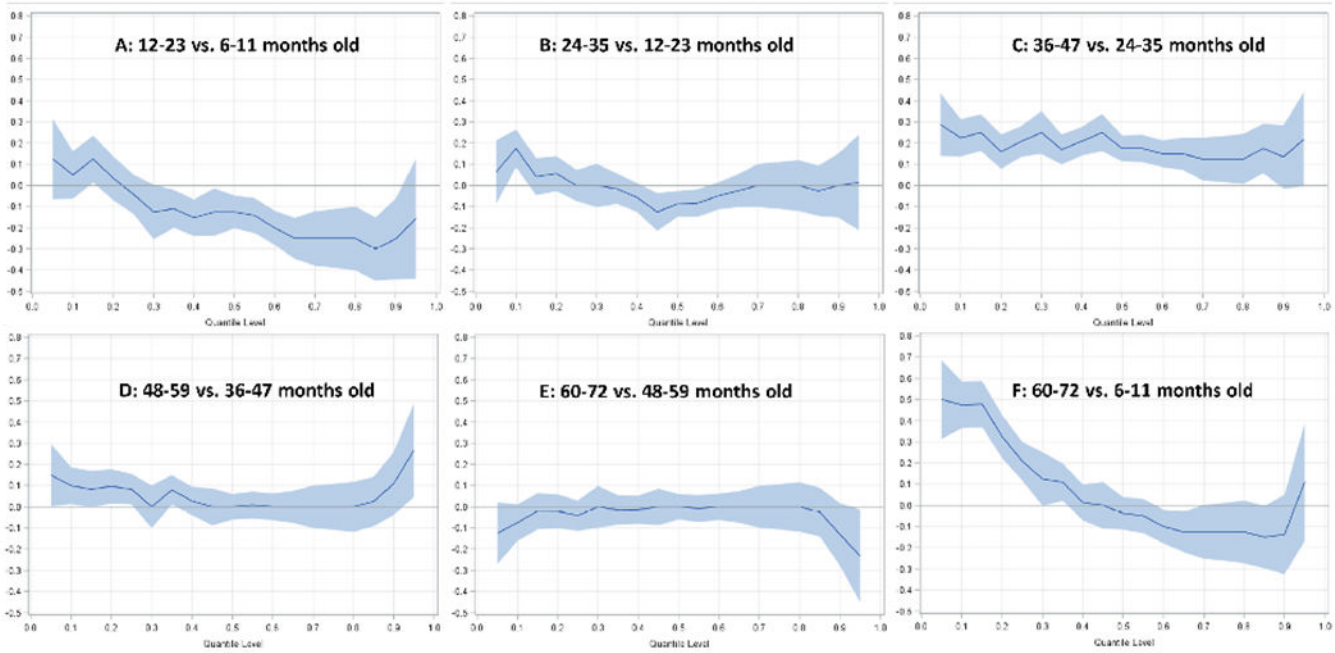

Figure 1. Quantile Regression Plots (a-f) Demonstrating the Estimated Effect of Age Across the Distribution of Refractive Errors (D) in Children 6 to 72 Months of Age.

The effect estimates were generated from multivariable quantile regression adjusted for other risk factors. The *x*-axis represents the quantile level (e.g., 0.1 = 10th percentile) of refractive error, and the *y*-axis represents the difference in corresponding refractive error between age groups (refractive error for older age group minus refractive error for younger age group). The shaded area represents 95 percent confidence intervals.

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Table 1.

Demographic Characteristics of Children with Cycloplegic Refraction Included in the Analysis of Hyperopia Prevalence

N (column percent)	BPEDS (Baltimore, MD, USA 2003-2007)	MEPEDS (Los Angeles, CA, USA 2003-2010)	STARS (Singapore 2006-2008)	SPEDS (Sydney, Australia 2007-2009)	Total
Overall	2231 (100%)	8448(100%)	2639(100%)	1733(100%)	**15051 (100%)**
Racial/ethnic groups					
Asian	27 (1%)	1309 (15%)	2639 (100%)	667 (38%)	**4642 (31%)**
African American	1194 (54%)	2861 (34%)	-	-	**4055 (27%)**
Hispanic white	140 (6%)	3003 (36%)	-	-	**3143 (21%)**
Non-Hispanic white	870 (39%)	1275 (15%)	-	1066 (62%)	**3211 (21%)**
Sex					
Male	1153 (52%)	4333 (51%)	1375 (52%)	934 (54%)	**7795 (52%)**
Female	1078 (48%)	4115 (49%)	1264 (48%)	799 (46%)	**7256 (48%)**
Age (months)					
6-11	164 (7%)	660 (8%)	163 (6%)	209 (12%)	**1196 (8%)**
12-23	351 (16%)	1467 (17%)	451 (17%)	259 (15%)	**2528 (17%)**
24-36	426 (19%)	1532 (18%)	442 (17%)	325 (19%)	**2725 (18%)**
36-47	430 (19%)	1559 (18%)	513 (19%)	313 (18%)	**2815 (19%)**
48-59	451 (20%)	1570 (19%)	537 (20%)	304 (18%)	**2862 (19%)**
60-72	409 (18%)	1660 (20%)	533 (20%)	323 (19%)	**2925 (19%)**

Abbreviations: BPEDS = the Baltimore Pediatric Eye Disease Study; MEPEDS = the Multiethnic Pediatric Eye Disease Study; STARS = the Strabismus, Amblyopia and Refractive Error in Singaporean Children Study; SPEDS = the Sydney Pediatric Eye Disease Study.

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Table 2.

Prevalence of Hyperopia Severity in the Worse Eye by Race/ethnicity, Sex, and Age of Child

		Any hyperopia (≥2.0 D)	Low/moderate hyperopia (2.0 D to < 4.0 D)		Moderate/high hyperopia (≥4.0 D)	
	N	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Overall	3086	20.5% (19.9%-21.2%)	2604	17.3% (16.7%-17.9%)	482	3.2% (2.9%-3.5%)
Race/Ethnicity						
Non-Hispanic white	884	27.5% (26.0%-29.1%)	748	23.3% (21.8%-24.8%)	136	4.2% (3.6%-5.0%)
Hispanic white	838	26.7% (25.1%-28.3%)	679	21.6% (20.2%-23.1%)	159	5.1% (4.3%-5.9%)
African American	824	20.3% (19.1%-21.6%)	695	17.1% (16.0%-18.3%)	129	3.2% (2.7%-3.8%)
Asian	540	11.6% (10.7%-12.6%)	482	10.4% (9.5%-11.3%)	58	1.3% (1.0%-1.6%)
P for race/ethnic difference[1]		<0.001		<0.001		<0.001
Sex						
Male	1476	18.9% (18.1%-19.8%)	1227	15.7% (14.9%-16.6%)	249	3.2% (2.8%-3.6%)
Female	1610	22.2% (21.2%-23.2%)	1377	19.0% (18.1%-19.9%)	233	3.2% (2.8%-3.6%)
P for sex difference[1]		<0.001		<0.001		<0.96
Age						
6-11	323	27.0% (24.5%-29.6%)	286	23.9% (21.5%-26.4%)	37	3.1% (2.2%-4.2%)
12-23	502	19.9% (18.3%-21.5%)	447	17.7% (16.2%-19.2%)	55	2.2% (1.6%-2.8%)
24-35	512	18.8% (17.3%-20.3%)	434	15.9% (14.6%-17.4%)	78	2.9% (2.3%-3.6%)
36-47	581	20.6% (19.2%-22.2%)	484	17.2% (15.8%-18.6%)	97	3.5% (2.8%-4.2%)
48-59	593	20.7% (19.3%-22.3%)	470	16.4% (15.1%-17.8%)	123	4.3% (3.6%-5.1%)
60-72	575	19.7% (18.2%-21.2%)	483	16.5% (15.2%-17.9%)	92	3.2% (2.5%-3.8%)
P for age trend[1]		0.012		<0.001		0.007

Abbreviation: CI=confidence interval.

[1]P values for race/ethnic and sex differences were estimated from chi-square tests and the P values for age trends were estimated from Mantel-Haenszel chi-square tests. 95% confidence interval values were estimated based on the exact method.

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Table 3.

Ocular Characteristics of Children with Different Levels of Hyperopia in the Worse Eye

	Emmetropia or nonsignificant hyperopia (0.5D to <2.0D)	Low/moderate hyperopia (2.0 D to <4.0 D)	Moderate/high hyperopia (≥4.0 D)	P[4]
N[1]	10443	2589	481	
N (%) with hyperopia in both eyes[1]	-	1759 (67.9%)	310 (64.4%)	0.14
RE of the worse eye, mean ± SD	0.96±0.54 D	2.59±0.54 D	5.19±1.33 D	-
RE of the better eye, mean ± SD	0.74±0.55 D	2.23±0.59 D	4.36±1.51 D	-
Interocular difference in RE, mean ± SD	0.22±0.21 D	0.36±0.38 D	0.82±0.90 D	<0.001
N (%) with spherical anisometropia (≥1.0 D)	90 (0.9%)	165 (6.4%)	139 (28.9%)	<0.001
N (%) with astigmatism (≥1.5 D)	542 (5.2%)	264 (10.2%)	94 (19.5%)	<0.001
N (%) with either spherical anisometropia or astigmatism[2]	619 (5.9%)	395 (15.3%)	213 (44.3%)	<0.001
Among children aged 3-5 years				
N (%) with either spherical anisometropia or astigmatism[2]	327 (5.3%)	210 (14.6%)	134 (43.0%)	<0.001
N (%) of children wearing glasses[3]	50 (1.0%)	30 (2.6%)	45 (17.6%)	<0.001
Axial length (mm)	22.2±0.7	21.6±0.7	20.8±0.7	<0.001
Corneal power (D)	44.0±1.5	43.9±1.6	43.7±1.5	<0.001
Corneal curvature radius (mm)	7.68±0.27	7.70±0.28	7.74±0.26	<0.001
Axial length/corneal curvature radius	2.89±0.07	2.81±0.07	2.69±0.08	<0.001

Abbreviation: SD = standard deviation.

[1] Data on bilateral involvement were missing for 101 children due to missing refraction data from one eye.

[2] Astigmatism of 1.5 D or greater

[3] Data on glasses wearing were not collected for 1483 children aged 36-72 months.

[4] P values for dichotomous and continuous variables were estimated using Mantel-Haenszel chi-square and analysis of variance tests.

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Table 4.

Multivariable Analyses of Risk Factors Associated with Different Severities of Hyperopia in the Worse Eye

	Total N of participants	Low/moderate Hyperopia (2.0 D to <4.0 D)			Moderate / High Hyperopia (≥4.0 D)		
		%	OR (95% CI)[1]	P[1]	%	OR (95% CI)[1]	P[1]
Race							
Asian	3584	10.3%	1.00 (ref)	-	1.3%	1.00 (ref)	-
African American	3351	16.9%	1.19 (0.98-1.44)	0.082	3.3%	1.27 (0.83-1.93)	0.28
Hispanic white	2958	21.5%	1.68 (1.37-2.05)	<0.001	5.1%	1.97 (1.28-3.03)	0.002
Non-Hispanic white	2291	24.4%	2.16 (1.78-2.61)	<0.001	4.4%	2.32 (1.52-3.52)	<0.001
Sex							
Male	6316	16.0%	1.00 (ref)		3.3%	1.00 (ref)	
Female	5868	19.1%	1.26 (1.14-1.39)	<0.001	3.4%	1.09 (0.89-1.33)	0.42
Age							
6-11	1018	24.0%	1.51 (1.25-1.81)	<0.001	2.9%	0.87 (0.56-1.34)	0.52
12-23	2108	17.4%	0.99 (0.84-1.15)	0.85	2.2%	0.59 (0.41-0.86)	0.006
24-35	2230	16.0%	0.89 (0.76-1.05)	0.16	2.9%	0.77 (0.55-1.08)	0.13
36-47	2229	17.4%	1.01 (0.86-1.18)	0.94	3.7%	1.05 (0.77-1.44)	0.76
48-59	2267	16.6%	0.97 (0.83-1.14)	0.70	4.5%	1.30 (0.96-1.75)	0.091
60-72	2332	17.2%	1.00 (ref)	-	3.5%	1.00 (ref)	-
Study							
STARS (Singapore)	2112	8.7%	1.00 (ref)	-	0.7%	1.00 (ref)	-
SPEDS (Sydney, Australia)	1026	16.5%	1.24 (0.95-1.62)	0.12	2.4%	2.28 (1.09-4.78)	0.028
BPEDS (Maryland, US)	1772	21.8%	1.79 (1.38-2.32)	<0.001	3.4%	3.18 (1.58-6.42)	0.001
MEPEDS (California, US)	7274	19.2%	1.75 (1.40-2.19)	<0.001	4.2%	4.48 (2.36-8.49)	<0.001
Family history of Strabismus							
No	11763	17.3%	1.00 (ref)	-	3.3%	1.00 (ref)	-
Yes	421	22.6%	1.20 (0.94-1.52)	0.14	5.7%	1.54 (1.00-2.38)	0.050
Educational level of primary caregiver							
≥College graduate	2565	14.7%	1.00 (ref)	-	2.4%	1.00 (ref)	-
High school graduate	6636	17.8%	1.16 (1.01-1.33)	0.032	3.3%	1.20 (0.88-1.63)	0.26
< High school	2983	19.1%	1.16 (0.98-1.37)	0.082	4.3%	1.32 (0.92-1.90)	0.13
Maternal smoking during pregnancy							
No	11360	17.0%	1.00 (ref)	-	3.2%	1.00 (ref)	-
Yes	824	23.7%	1.28 (1.07-1.54)	0.007	5.2%	1.64 (1.16-2.33)	0.005
Number of cigarettes per day[2]							
0	11360	17.0%	1.00 (ref)	-	3.2%	1.00 (ref)	-
1 to <5	336	22.3%	1.26 (0.96-1.65)	0.091	5.4%	1.72 (1.04-2.83)	0.035
≥5	437	25.2%	1.34 (1.06-1.70)	0.015	5.3%	1.62 (1.02-2.58)	0.040
Period of smoking[2]							

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	Total N of participants	Low/moderate Hyperopia (2.0 D to <4.0 D)			Moderate / High Hyperopia (≥4.0 D)		
		%	OR (95% CI)[1]	P[1]	%	OR (95% CI)[1]	P[1]
Nonsmokers	11360	17.0%	1.00 (ref)	-	3.2%	1.00 (ref)	-
1st or 2nd trimester only	349	25.5%	1.44 (1.12-1.86)	0.005	3.7%	1.17 (0.66-2.08)	0.59
3rd trimester	463	22.9%	1.21 (0.95-1.53)	0.13	6.3%	2.03 (1.32-3.11)	0.001
Duration of smoking, months[2]							
0	11360	17.0%	1.00 (ref)	-	3.2%	1.00 (ref)	-
>0 to ≤3	317	25.9%	1.45 (1.11-1.89)	0.006	3.5%	1.10 (0.59-2.05)	0.77
4 to 6	88	22.7%	1.24 (0.74-2.07)	0.42	5.7%	1.79 (0.71-4.52)	0.22
7 to 9	413	22.5%	1.19 (0.93-1.53)	0.17	6.5%	2.11 (1.36-3.28)	<0.001
Cigarette-Months of smoking[2]							
0	11360	17.0%	1.00 (ref)	-	3.2%	1.00 (ref)	-
>0 to <9	180	27.2%	1.61 (1.15-2.27)	0.006	4.4%	1.49 (0.72-3.09)	0.28
9 to <45	304	21.7%	1.17 (0.88-1.56)	0.28	4.6%	1.41 (0.80-2.48)	0.24
≥45	287	24.7%	1.30 (0.97-1.73)	0.079	6.6%	2.11 (1.26-3.52)	0.005

Abbreviations: BPEDS = the Baltimore Pediatric Eye Disease Study; CI=confidence interval; D=diopter; MEPEDS = the Multiethnic Pediatric Eye Disease Study; OR=odds ratio; STARS = the Strabismus, Amblyopia and Refractive Error in Singaporean Children Study; SPEDS = the Sydney Pediatric Eye Disease Study.

[1]Odds ratios (ORs), 95% confidence intervals (CIs) and p values were estimated from multivariable polytomous logistic regression with severity of hyperopia (categorized as emmetropia or nonsignificant hyperopia, low/moderate hyperopia, and moderate/high hyperopia) as the outcome variable. Estimates for each of the maternal smoking parameters were generated from multivariable regression models replacing the binary smoking status variable with the corresponding categorical variable and adjusting for all other non-smoking covariates.

[2]Cigarette-months of smoking was calculated as the product of number of cigarettes smoked per day and the number of months of smoking during pregnancy. Data on number of cigarettes smoked per day, period of smoking, duration of smoking, and cigarette-months were missing for ≤53 participants.