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THE GLENN A. FRY AWARD LECTURE (1995)

Myopia Development in Childhood

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ABSTRACT: *Purpose.* The Orinda Longitudinal Study of Myopia is a 12-year project examining predictive factors for the onset of myopia, the underlying etiologies of myopia, and normal eye growth in school children. *Methods.* This paper reports on all measurements made of the ocular components (cycloplegic refractive error, corneal curvature, crystalline lens power, and axial ocular dimensions), parental history of myopia, and near work activity in children participating in the Orinda Longitudinal Study of Myopia between 1989 and 1993. An analysis of the interaction between parental history of myopia and children's near work is conducted on the cross-sectional study data from 1993. *Results.* The cross-sectional and longitudinal data show a gradual decrease in refractive error from low hyperopia toward emmetropia, no shift in corneal curvature, a gradual decrease in crystalline lens power, thinning of the crystalline lens, and elongation of the eye between the ages of 6 and 14 years. Parental history is more contributory to a statistical model predicting myopia than is near work, but near work is a significant factor as well. We can find no evidence of statistical interaction between parental history and near work in explaining the presence or absence of myopia. *Conclusions.* The emmetropization process is evident in the gradual decrease in refractive error toward emmetropia, the axial elongation of the eye, and the compensating decrease in crystalline lens power. Both nature and nurture play a role in the etiology of myopia, although the predominant role appears to belong to a positive parental history of myopia. This role does not appear to be through an interaction between parental myopia status and children's near work activity. (Optom Vis Sci 1997;74:603–608)

Myopia, or nearsightedness, occurs with a general population prevalence as high as 25% in the United States[1] and 40 to 60% in Asia.[2, 3] One recent report in adults has shown a decreasing prevalence of myopia in younger adults, from 43% of 40- to 49-year-olds to only 14% of 70- to 79-year-olds.[4] Juvenile onset myopia is most likely to develop between the ages of 8 and 14 years.[5] The field of myopia has generated considerable interest with the advent of photorefractive surgery,[6] and the specific health care and general societal costs of myopia correction—however it is accomplished—are high.[7]

As treatments for myopia have been pursued, conflicting theories exist as to its etiology. Classically, these theories can be summarized as nature versus nurture, i.e., a genetic theory versus an environmental theory in which near work and reading cause the axial ocular elongation of myopia.[8]

Earlier evidence for the influence of genetics includes an increased prevalence of myopia among children of myopic parents[9, 10] and a greater similarity in refractive error and its underlying optical, ocular components among monozygotic twins compared with dizygotic twins.[11–13] Lines of support for an environmental influence in the form of excess near work[14] come from epidemiological evidence of the increasing prevalence of myopia with increasing education and higher amounts of near work[15–18] and from the profound influence the visual environment can have on the development of myopia in animal models.[19]

METHODS

The Orinda Longitudinal Study of Myopia

The methods used in the Orinda Longitudinal Study of Myopia have been described in detail elsewhere.[10, 20] It is a community-based study in that the testing sessions take place on the campuses of the four schools in the Orinda Union School District. The study was initiated in 1989 and is slated to continue through 2001. Children participate in the study after they and their parents receive an explanation of all study procedures, and parents give informed consent according to the protocol approved by the Committee for the Protection of Human Subjects of the University of California, Berkeley.

Subjects

As of the end of 1995, 1,246 children were enrolled in the study, representing 48% participation of eligible children. Losses to follow-up have averaged approximately 1% per year. The data for all children tested in 1993, the fifth year of the study, are reported here. This volunteer sample comprises 716 children who range in

age from 6.0 to 14.90 years. The mean age is 9.7 years with a standard deviation of 2.4 years.

Ocular component measurements

We measured the right eye's ocular components and refractive error on the subject sample as described previously in detail.[20] Specifically, we used the Canon R-1 autorefractor to measure refractive error, the KERA CorneaScope to measure corneal power, a videophakometer to measure crystalline lens curvatures,[21] and A-scan ultrasonography to measure axial ocular dimensions. To facilitate the measurements, topical 0.5% proparacaine was instilled before the mydriatic agent was instilled and again just before ultrasonography, and topical 1% tropicamide was instilled (2 drops 5 min apart with measurements 25 min after the 2nd drop) to induce corneal anesthesia, pupillary mydriasis, and cycloplegia. All measurements were conducted without examiner knowledge of the child's visual activity profile or parental history of myopia. A particular child was defined as myopic if he or she had refractive error of at least −0.75 D in both principal meridians of the eye.

Parental survey

The parents of children in the study were surveyed at enrollment and annually by mail to document the children's medical and ocular history, to assess the children's visual activity profile, and to determine the parents' myopia status. The formula used to create the variable, "diopter-hours," was as follows: diopter-hours = 3 × hours spent reading (for pleasure or studying) + 2 × hours spent playing video-type games + hours spent watching television. This represents an attempt to weight the child's visual activities according to the amount of accommodation in diopters (D) required to perform them. We have assumed validity of the parents' reports of their children's visual activities based on other studies' validation of parents as proxies for children on questionnaires.[22, 23]

A parent was classified as myopic if he or she reported that he or she wore glasses that were primarily for distance viewing or he or she wore glasses that were equally important for distance and near viewing as long as the glasses had been prescribed before age 16 years. It is reasonable to assume that parents have accurately reported whether the child's natural parents wear corrective lenses, the reasons for correction (i.e., for distance and/or near viewing), and the year corrective lenses were first prescribed. At least one previous study has used questions similar to these to accurately classify patients as myopic compared with eye examination data.[24] Studies indicate that medical data are more likely to be reported accurately by respondents when the medical condition represents a significant "life event" or itself is serious or distinctive with clear diagnostic criteria and when the condition affects in some way the person's everyday activities.[25–27] The correction of refractive error satisfies these criteria.

Statistical methods

Multiple logistic regression was performed using SAS version 6.07,[28] modeling the risk of having one or more myopic parents on the child's myopia, adjusting for age and near work (diopter-hours). Parental myopia is a categorical variable, and age and near work (diopter-hours) are treated as continuous variables.

We fit the cubic growth curve to these data by maximum likelihood estimation using a mixed model analysis of covariance,[29] which accounts for the correlation between repeated measurements on the same subject through a compound symmetry covariance structure. The model assumes that, for each subject, the population growth curves displayed are: (1) shifted by a random, child-specific amount (the variance of which accounts for the between-child variability), and (2) perturbed over time by measurement error and lability in lens thickness (leading to within-child variability). To choose the shape of the growth curve, we fit a nested series of polynomials ranging in order from 0 (representing no trend in lens thickness with age) to 4 (representing a quartic trend).

RESULTS

Figure 1 compares our prevalence for data by noncycloplegic retinoscopy from the Orinda Longitudinal Study of Myopia children examined in 1993 with prevalence data from the original study conducted in Orinda between 1954 and 1956.[5] An increased prevalence of myopia from a maximum of 12% in 13-year-olds in the 1950s to a maximum of 20% in 1993 appears across ages using similar criteria (at least −0.50 D of myopia in both meridians) and is retained even using our more stringent criterion for myopia (at least −0.75 D of myopia in both meridians). We now believe this may be related to the changing ethnic demographics of this community during the past 30 to 40 years.

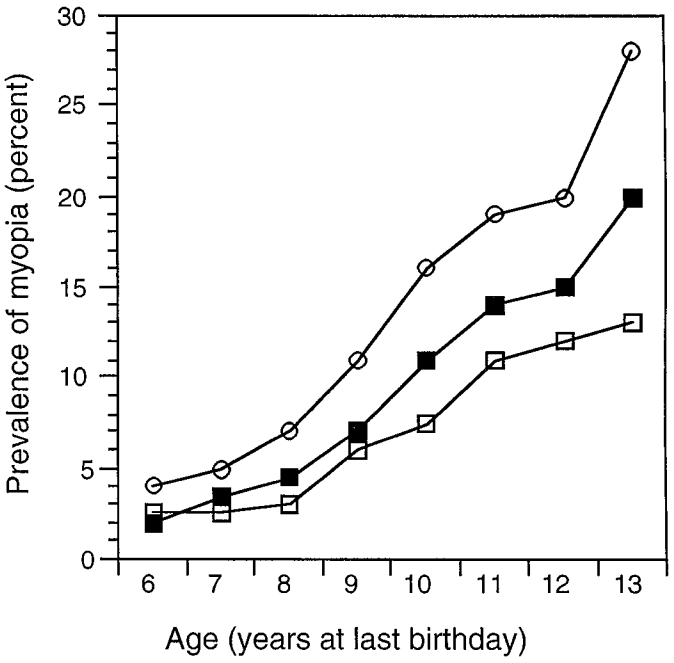

FIGURE 1.
The prevalence of myopia (by a criterion of at least −0.50 D in both meridians as measured by noncycloplegic retinoscopy) in Orinda, California in 1954 through 1956 is denoted by the open squares. The open circles depict the use of that same criterion from data collected on Orinda Longitudinal Study of Myopia children in 1993, and the filled squares are from Orinda Longitudinal Study of Myopia children in 1993 using a criterion of at least −0.75 D of myopia in both meridians as measured by noncycloplegic retinoscopy.

Figures 2 through 6 show ocular component data collected from 1989 through 1993 as a function of age. Refractive error in the vertical meridian declines, on average, from low hyperopia toward emmetropia with increasing age (Fig. 2), with the typical distribution, leptokurtic for near emmetropia and more myopes than hyperopes, evident. The summary curve for central corneal curvature in the vertical meridian shows no effect with age (Fig. 3). The previously reported thinning of the crystalline lens between the ages of 6 and 9 years[30] is evident in Fig. 4. Figure 5 shows the typical decrease in crystalline lens power occurring during school ages, presumably to compensate for the axial length increases that occur concurrently (Fig. 6).

After excluding children from the dataset who met our criteria for myopia [22/180 (12.2%) of the children with two myopic parents, 26/316 (8.2%) of the children with one myopic parent, and 6/220 (2.7%) of the children with no myopic parents, 54 children in total], we reported previously that children (presumably at some greater risk for myopia because they have two myopic parents) have longer eyes and less hyperopic refractive error than children with only one myopic parent or no myopic parents. Further, we modeled refractive error as a continuous variable by age, parental history of myopia, and children's near work and found that parental history was a much greater contributor than children's near work to the prediction of children's refractive error and the ocular components that contribute to it. However, near work was a statistically significant factor in the model.[10]

That report triggered a lively discussion, both in and out of print.[31–33] Issues raised included whether the nature versus nurture debate for the etiology of myopia is a nature and nurture debate, but in two very specific ways: (1) Do myopic parents actually produce myopic school-aged children by creating a myopigenic environment in that the parents encourage and reward children's near work, reading, etc.? or (2) Is what children inherit actually a susceptibility to their environment so that if they have myopic parents they are more prone to the deleterious effects of near work? These two alternative explanations for our previously reported results are examples of statistical confounding and interaction respectively and are depicted in Figs. 7 and 8.

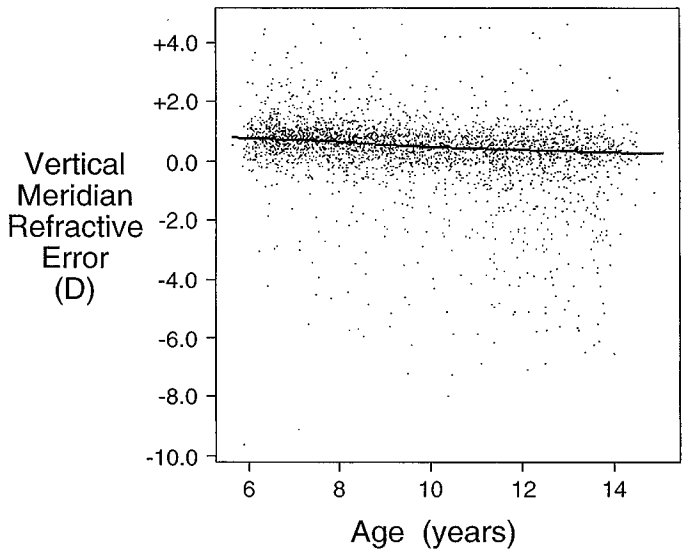

FIGURE 2.
Cross-sectional and longitudinal data from the Orinda Longitudinal Study of Myopia from 1989 through 1993 showing the distribution of refractive error (cycloplegic autorefractor results in the vertical meridian) with age, depicting emmetropization on average.

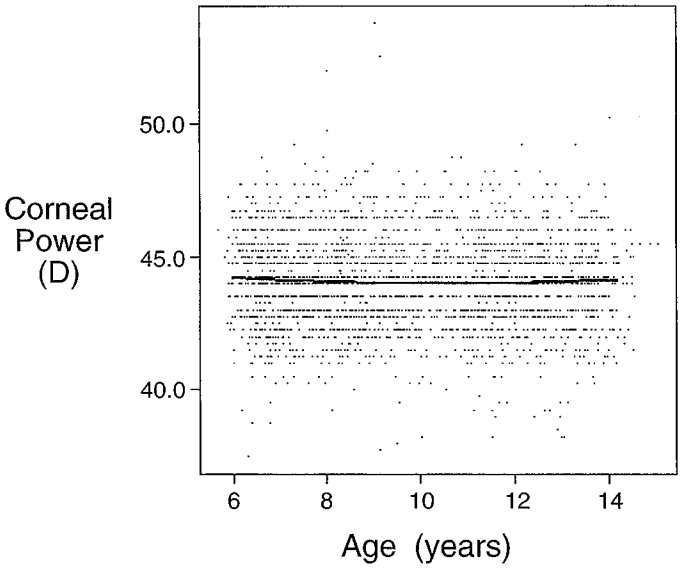

FIGURE 3.
Cross-sectional and longitudinal data from the Orinda Longitudinal Study of Myopia from 1989 through 1993 showing the distribution of corneal curvature (vertical meridian).

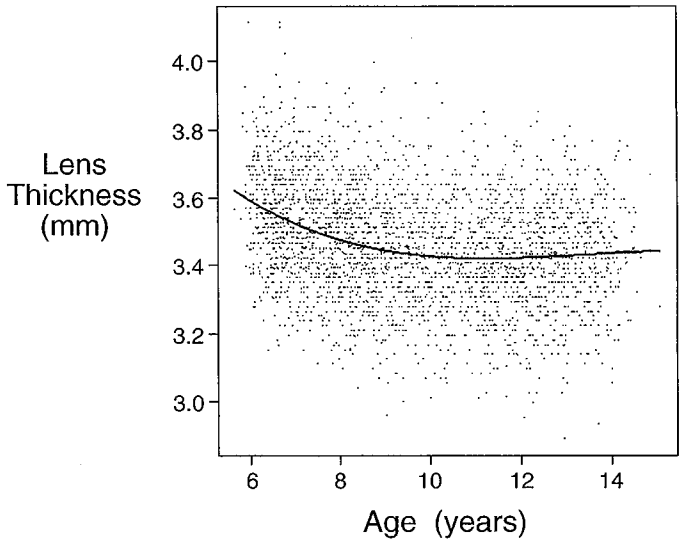

FIGURE 4.
Cross-sectional and longitudinal data from the Orinda Longitudinal Study of Myopia from 1989 through 1993 showing the distribution of the axial dimension of the crystalline lens as measured by A-scan ultrasonography. The lens thins between the ages of 6 and 9 years.

We first examined these data to verify the previous result of an increased risk of myopia with increasing number of myopic parents. Controlling for diopter-hours and child's age, the odds ratio for having one myopic parent compared with having no myopic parents was 1.32 (95% CI, 0.60 to 2.91). The odds ratio for having two myopic parents compared with having no myopic parents was 5.12 (95% CI, 2.37 to 11.10). These results confirm an increased risk of myopia in children with two myopic parents.

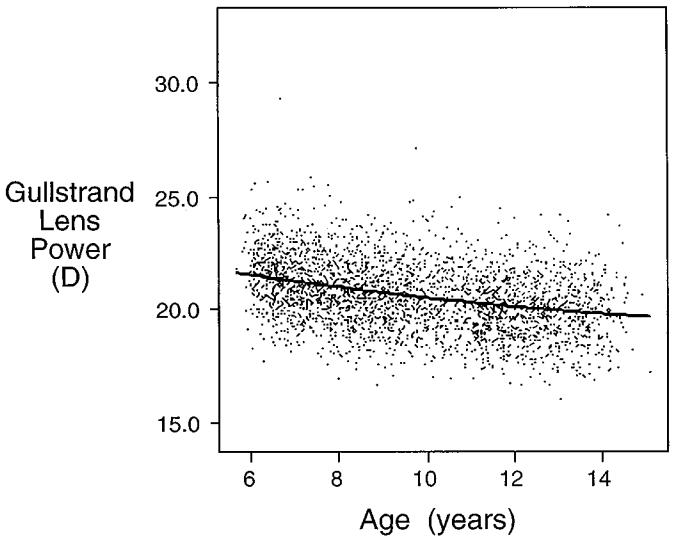

FIGURE 5.

Cross-sectional and longitudinal data from the Orinda Longitudinal Study of Myopia from 1989 through 1993 showing the distribution of crystalline lens power (vertical meridian) calculated from videophakometric measurements[21, 36] showing steadily decreasing power between the ages of 6 and 14 years.

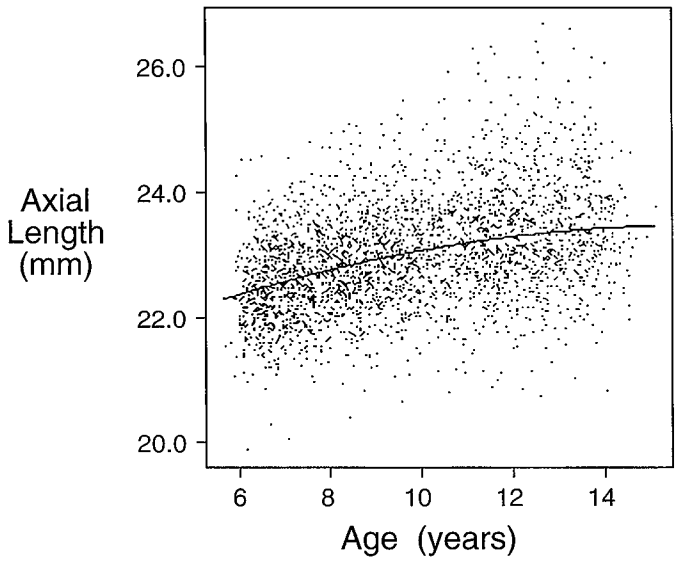

FIGURE 6.

Cross-sectional and longitudinal data from the Orinda Longitudinal Study of Myopia from 1989 through 1993 showing the distribution of axial length as measured by A-scan ultrasonography showing overall ocular growth between the ages of 6 and 14 years.

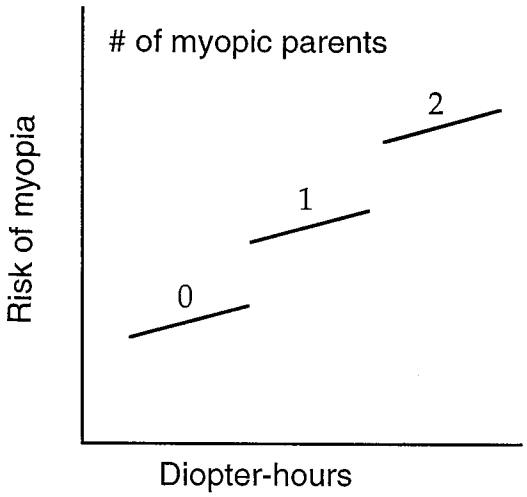

FIGURE 7.

The relationship between risk of myopia and near work is present and constant, but the risk of myopia increases with an increasing number of myopic parents.

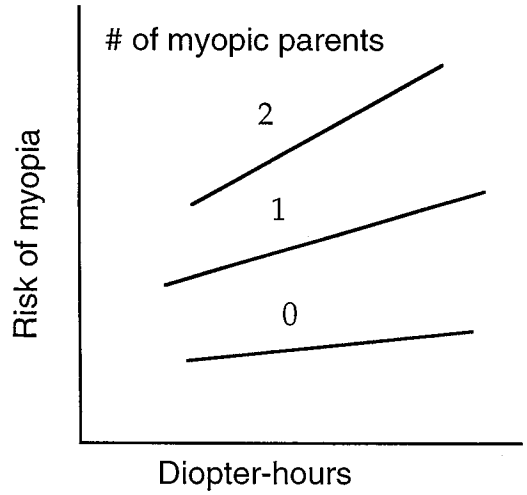

FIGURE 8.

The risk of myopia increases with an increasing number of myopic parents, as does the risk of myopia for a given amount of near work.

If Fig. 7 were an accurate depiction of how parental history of myopia and near work confound their respective roles in the etiology of myopia, we would expect the odds ratios for the risk of myopia given one or two myopic parents to shift with the adjustment for near work. In fact, the odds ratio for one myopic parent when unadjusted for near work is 1.44 (95% CI, 0.66 to 3.14) and for two myopic parents when unadjusted for near work is 5.62 (95% CI, 2.61 to 12.10). The expected shift in risk for myopia with near work as hypothesized in Fig. 7 does not occur.

Similarly, the odds ratio for a one (natural) log unit increase in near work as denoted by diopter-hours, controlling for parental history of myopia and child's age, was 1.49 (95% CI, 0.86 to 2.56). This confirms the previous result of a minimal role for near work as a risk factor for juvenile onset myopia. If Fig. 8 is an accurate picture of the increasing role of near work with an increasing number of myopic parents, then we would expect the odds ratio for a one (natural) log unit increase in diopter-hours to increase in a "dose-response" fashion with the number of myopic parents. Table 1 shows the odds ratios from this analysis. The odds ratio for a one (natural) log unit increase in diopter-hours does not increase with the number of myopic parents. The lowest odds ratio in Table 1 is for the children most at risk for the proposed genetic susceptibility to the environment—those with two myopic parents. These results do not support theories whereby parental history of myopia and near work confound one another or statistically interact with one another to produce juvenile onset myopia.

TABLE 1.
Effect of a one log unit increase in near work as measured by diopter-hours.

No. of Myopic Parents	Odds Ratio	95% Confidence Interval
2	0.96	0.43, 2.12
1	2.48	0.97, 6.38
0	1.72	0.51, 5.82

DISCUSSION

There is great interest in determining the cause of school-aged myopia. The high prevalence of myopia in the United States reaches almost epidemic proportions in Asia. The contact lens industry, traditional refractive surgery procedures, and the recent advent of excimer laser-based treatments for refractive surgery are big business in the world today. At least seven patents for pharmacological agents for the control of eye growth—and presumably the treatment of myopia—have been filed in the United States alone.

Our cross-sectional and longitudinal data on normal eye growth in children comprise the largest dataset ever assembled. Our data document conclusively the emmetropization process that includes ocular component compensation for the elongating eye during the school years. That compensation by the anterior segment of the eye occurs in the form of crystalline lens thinning, crystalline lens surface flattening, and crystalline lens power decrease, not in corneal flattening.

Our previous report of a dominant role for genetics in the etiology of juvenile onset myopia also documented a smaller role for environmental factors in the form of near work.[10] Recent evidence from animal models of myopia lend support to the environmental theories, but the usual arguments about the degree of translation possible from chicken, tree shrew, and primate models of myopia in neonatal animals to school-aged human children exist.[19] The eventual efficacy of a topical medication for myopia may conceivably depend on the underlying etiology of myopia, either overall or in a particular child. For example, if a child's near work habits can be changed to eliminate or reduce the environmental risk of myopia, it may be that a topical medication could also be prescribed to control his or her genetic risk.

Studies in twins have been quoted as demonstrating an interaction between parental history of myopia and environmental factors.[34, 35] Instead, one of these studies shows an interaction between zygosity (not history of myopia) and environmental factors,[35] and the other simply refers to the possibility of such an interaction.[34] These results show that theories calling for complex relationships between the genetic and environmental influences that mitigate the direct genetic influence are not supported by our data. Although it may be true that some small degree of the genetic effect on abnormal axial eye elongation and, therefore, myopia development, is through behavioral manifestations, these negative results do not paint a picture whereby the entire influence of having one or two myopic parents is through how much they encourage a child to read.

Future plans for the Orinda Longitudinal Study of Myopia include analysis of predictors for the onset of myopia in children well before the onset of that myopia occurs. This will entail comparing initial refractive error, ocular component values, parental history of myopia, near work, and other candidate factors in children who develop myopia during the course of the study to those same factors in children who do not develop myopia during the course of the study. Other planned studies include the collection of genetic material from myopic children enrolled in the study and their families to attempt to sequence the gene or genes that may be contribute to the etiology of juvenile onset myopia. And, in the fall of 1997, three clinical centers will be added to the new Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study at the West Alabama Health Center, the University of Houston College of Optometry, and the Southern California College of Optometry to examine the differences between African-American, Hispanic, and Asian children, respectively.

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