The Contributions of Near Work and Outdoor Activity to the Correlation Between Siblings in the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study

Lisa A. Jones-Jordan,[1] Loraine T. Sinnott,[1] Nicholas D. Graham,[2] Susan A. Cotter,[3] Robert N. Kleinstein,[4] Ruth E. Manny,[5] Donald O. Mutti,[1] J. Daniel Twelker,[6] and Karla Zadnik,[1] for the CLEERE Study Group

[1]The Ohio State University College of Optometry, Columbus, Ohio, United States
[2]Private Practice, Matthews, North Carolina, United States
[3]Marshall B. Ketchum University, Fullerton, California, United States
[4]University of Alabama at Birmingham School of Optometry, Birmingham, Alabama, United States
[5]University of Houston College of Optometry, Houston, Texas, United States
[6]University of Arizona Department of Ophthalmology and Vision Science, Tucson, Arizona, United States

Correspondence: Lisa A. Jones-Jordan, The Ohio State University College of Optometry, 649 Fry Hall, 338 West 10th Avenue, Columbus, OH 43210, USA; Jordan.646@osu.edu.

See the appendix for the members of the CLEERE Study Group.

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Purpose. We determined the correlation between sibling refractive errors adjusted for shared and unique environmental factors using data from the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study.

Methods. Refractive error from subjects' last study visits was used to estimate the intraclass correlation coefficient (ICC) between siblings. The correlation models used environmental factors (diopter-hours and outdoor/sports activity) assessed annually from parents by survey to adjust for shared and unique environmental exposures when estimating the heritability of refractive error (2*ICC).

Results. Data from 700 families contributed to the between-sibling correlation for spherical equivalent refractive error. The mean age of the children at the last visit was 13.3 ± 0.90 years. Siblings engaged in similar amounts of near and outdoor activities (correlations ranged from 0.40–0.76). The ICC for spherical equivalent, controlling for age, sex, ethnicity, and site was 0.367 (95% confidence interval [CI] = 0.304, 0.420), with an estimated heritability of no more than 0.733. After controlling for these variables, and near and outdoor/sports activities, the resulting ICC was 0.364 (95% CI = 0.304, 0.420; estimated heritability no more than 0.728, 95% CI = 0.608, 0.850). The ICCs did not differ significantly between male–female and single sex pairs.

Conclusions. Adjusting for shared family and unique, child-specific environmental factors only reduced the estimate of refractive error correlation between siblings by 0.5%. Consistent with a lack of association between myopia progression and either near work or outdoor/sports activity, substantial common environmental exposures had little effect on this correlation. Genetic effects appear to have the major role in determining the similarity of refractive error between siblings.

Keywords: myopia, pediatric, heritability

The search for the respective contributions of genetics and environment to the development of juvenile-onset myopia continues. Two recent reports from molecular genetic studies on the largest samples yet tested identified 35 possible loci associated with myopia.[1,2] There is ample evidence for a genetic component to refractive error.[3,4] Cross-sectional and longitudinal studies have shown an increased odds of myopia in children with increasing numbers of myopic parents,[5–7] which may be altered by the amount of time spent in outdoor/sports activities. Data from children with two myopic parents, who constitute a group at high risk for myopia development, revealed that performing more hours of outdoor/sports activity led to a decrease in the occurrence of myopia compared to children with two myopic parents who performed a minimal amount of outdoor/sports activity. This high risk group had a similar probability of developing myopia as those without myopic parents when the level of time in outdoor/sports activity was in the highest quartile.[8]

The genetic contribution to a trait often is estimated through heritability. Heritability is the proportion of phenotypic variability in a population trait that is due to genetic differences. Twin studies have found high refractive error heritabilities ranging from approximately 0.77 to 0.94.[3,4,9,10] One of the lower estimates from a twin study was reported by Tsai et al.[11] who found heritability of 0.33 for refractive error, but heritability of 0.67 for axial length in a predominantly myopic

sample of twins. One limitation of this study was the small number of dizygotic twin pairs (17) and the need for adult subjects to remember back to kindergarten, primary school, and high school for near work covariate data. Other studies have used siblings[12,13] or parents–offspring with siblings and other familial pairs,[14] and found refractive error heritability from 0.50 to 0.70. These studies indicate that a large proportion of the variance in refractive error may be attributable to genetics.

Analyses using variance components methodology allow for the calculation of additional subsets of the variance, which can characterize the contributions of common (or shared) or unique environmental effects, as well as potential dominant effects. Chen et al.[14] found that a genetic model with common and unique environmental effects best fit the data, and estimated the proportion of the variance explained by the common environment at 0.33 for refractive error when examining a model of siblings (i.e., shared childhood environment). Lopes et al.[9] also found this model to be the best fit for their refractive error data with the estimated proportion of the variance explained by the common environment at 0.07 and the proportion of the variance explained by the unique environment at 0.16. Others have found that the best-fitting model for refractive error was the genetic and unique environment model, with the proportion of the variance explained by the unique environment between 0.09 and 0.14.[3,4] These shared and unique environmental influences, therefore, are estimated to be between 7% and 33% of the variance in refractive error.

Interestingly, these shared and unique environmental influences also are typically estimated through modeling rather than through the use of data collected on environmental exposures. Limited data are available that account for environmental influences that have been measured in children rather than estimated through modeling. Guggenheim et al.[15] used data from 306 subjects with at least one sibling also enrolled in the Singapore Cohort Study of the Risk Factors for Myopia (SCORM) to look at the correlation of refractive error between siblings. Subjects were enrolled between ages 7 and 9 years, and information from their last visit was used in the analyses. In addition to children's refractive error and ocular components, baseline information was collected about the number of hours per week spent in visual activities. None of the analyses of correlation between siblings, however, integrated the refractive error data with the visual activity data in an effort to estimate the impact of the visual activities on this correlation.

The Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study was a multicenter, longitudinal, observational study that evaluated the ocular component development and risk factors for juvenile-onset myopia in children of different ethnicities. Time spent performing near visual activities and outdoor/sports activities was collected by questionnaire on an annual basis. Many families enrolled multiple children in the study, thereby allowing for analyses of the correlation of refractive error between siblings. Here, we provided an estimate of the correlation between siblings for near and outdoor activities, as well as an estimate of the impact of the shared environmental factors on this correlation between refractive errors.

Methods

Subjects were children aged 6 to 14 years old in the CLEERE Study between 1989 and 2009. The Orinda Longitudinal Study of Myopia (Orinda, CA, USA) became CLEERE in 1997 with the addition of sites enrolling African-American children (Eutaw, AL, USA), Asian children (Irvine, CA, USA), and Hispanic children (Houston, TX, USA) children. In 2000, a site to enroll Native-American children (Tucson, AZ, USA) was added. Each affiliated university's institutional review board approved the protocol and informed consent documents in accordance with the tenets of the Declaration of Helsinki. In addition to obtaining parental consent, children provided assent.

Ethnic group identity was supplied by a parent on a CLEERE medical history form at enrollment into the study by choosing among six categories, based on National Institutes of Health (NIH; Bethesda, MD, USA) categories: American Indian or Alaskan Native, Asian or Pacific Islander, Black not of Hispanic origin, Hispanic, White not of Hispanic origin, other or unknown.

Visual activity data were provided annually using a questionnaire that asked the parent "During the school year, how many hours per week (outside of regular school hours) would you estimate this child: (1) studies or reads for school assignments, (2) reads for fun (pleasure), (3) watches TV, (4) uses a computer/plays video games, (5) engages in outdoor/sports activities?" Diopter-hours also were calculated as a comprehensive near work exposure, defined as: $3 \times$ hours of reading $+ 3 \times$ hours of studying $+ 2 \times$ video/computer hours $+$ hours watching television.[5] For these analyses, we focused on the contributions of outdoor/sports activity hours, reading hours, studying hours, and a combined variable, diopter-hours to the variability of refractive error.

Refractive error measurements were made on the right eye only by certified study personnel with the Canon R-1 autorefractor (Canon USA, Lake Success, NY, USA; no longer manufactured) from 1989 to 2000 and the Grand Seiko WR 5100-K autorefractor (Grand Seiko Co., Hiroshima, Japan) from 2001 to 2009. For cycloplegic autorefraction, subjects fixated on a reduced Snellen target through a +4.00 diopter (D) Badal lens in primary gaze. The Badal lens allowed the uncorrected subjects to fixate on an in-focus target during autorefraction without stimulating any residual accommodation. The Badal system allows for the correction of either hyperopic or myopic errors while keeping the retinal image size of the target constant.

For subjects with grade 1 or 2 iris color (in general, a blue or gray iris or with a green iris with a lesser amount of brown pigment),[16] testing was performed 30 minutes after one drop of proparacaine 0.5% and two drops of tropicamide 1.0%. When subjects had dark iris colors greater than grade 2, testing was performed 30 minutes after one drop of proparacaine 0.5% and one drop each of tropicamide 1.0% and cyclopentolate 1.0%.[17] Ten autorefractor measurements were made according to a standard protocol.[18]

Full siblings enrolled in this study were identified by the study coordinators at each site, and each family was assigned a family identification number to link siblings together. Some families had multiple children enrolled in the study. In these cases, all eligible siblings were included in the analysis.

We restricted the data to refractive error gathered at the last visit for each of the full sibling participants. Children in the sample had to be at least 10 years of age or older at their last visit. The last visit and the age restrictions were used to enhance the likelihood that there was indication of myopia in children who would become truly myopic and the measurements used were gathered when siblings were similar in age. Refractive error was analyzed as spherical equivalent.

The shared family level effects were estimated by averaging each sibling's longitudinal data, then averaging the sibling results together to get the family activity level. This approach allowed for the use of the pattern of activities over time without incorporating the complexity of time-varying covariates into the model. Family age was the average of the siblings'

Investigative Ophthalmology & Visual Science

ages at their last visit. For sex, males were coded with 0 and females 1, with family sex as the average of these two sibling indicators. The unique, child-level effects were estimated using the deviation of his/her individual average from the family average.

These activity levels then were used as covariates in the model for refractive error to adjust for environmental effects. The model had the following general form:

$$\text{SPHEQ}_{fc} = \text{A} + \text{B*Family Age} + \text{C*Sex} + \text{D*Ethnicity} + \text{E*Site} + \text{F*Outdoors} + \text{G*Diopter}-\text{hours} + \mu_f + \varepsilon_{fc},$$

where *f* indexes the family and *c* a child in that family. The μ and ε terms represent random effects on spherical equivalent refractive error of shared family and unique, child-level factors, respectively, that are not explained by the other measured covariates. Four of the covariates provided estimates of shared family level and unique, child-level effects: family age, sex, outdoor/sports hours, and diopter-hours.

The intraclass correlation coefficient (ICC) is a statistic that measures how strongly individuals in a family resemble each other. It is estimated by dividing the amount of the variance that is due to the relationship (between-sibling variance) by the total amount of variance. In other words, it is the ratio $\sigma^2_f/(\sigma^2_f+\sigma^2_c)$, where σ^2_f is the variation of the shared family-level effect (between-sibling variance) and σ^2_c is the variation of the within-family unique child-level effects (within-child variance). Multiplying the ICC by 2 provides an estimate of heritability because the genetic covariance between full siblings is equal to half of the total additive genetic variance.[19,20] This estimate is described throughout the rest of the study as an upper bound for heritability because other covariates, such as shared or unique environmental factors, could account for more variation, thereby inflating the estimate of heritability. An unadjusted ICC for spherical equivalent refractive error was estimated and then compared to the ICCs adjusted for covariates, such as age, sex, ethnicity, study site, near work, and time outdoors, that were added sequentially to assess their impact on ICC. The ICC and estimated upper bound on heritability are presented to facilitate comparison with literature that uses either terminology. In addition to using the full dataset to examine the ICC, families were analyzed by type of siblings (all sisters, all brothers, and brother/sister). All covariance estimation was done using the NLMIXED procedure in SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

In total, 847 full-sibling families were identified from the CLEERE Study. Of these 726 remained when the age criterion of "at least 10 years old at the last visit" was applied. Of the 726 families, 22 had inconsistent reports of ethnicity and were removed from the dataset. Only one family was classified as "Other" ethnicity, and this family was removed as well. Three more families were lost because of incomplete activity data. This left 700 families with 1522 children. The mean (±SD) number of siblings in a family was 2.2 (±0.5). Of these families, 85% were two-sibling families (Table 1). Of the family units, 44% were White, 14% African-American, 13% Asian, 7% Native American, and 22% Hispanic. At their last visit, the mean age (±SD) of children was 13.3 years (±0.90; range, 10.0–17.2), and more than half of the subjects were at least 14 years old at their last study visit. The mean last visit spherical equivalent refractive error was −0.42 D (±1.40; range, −12.2 to +10.10 D). The mean difference (±SD) in age between the oldest and youngest sibling at the last visit was 1.24 years (±1.01); that is, for most of the siblings that we used, their data spherical equivalent measurements were taken at their most similar ages. The Figure shows the correlation of refractive error between siblings in a family. For families with more than two siblings, data from the oldest and youngest siblings were plotted. The plot indicates medium concordance between the siblings' refractive errors ($r = 0.39$, $P < 0.0001$).

Table 1. Demographics

Variable	*N* (%)
Age at last visit, y	
10	52 (3.4)
11	108 (7.1)
12	151 (9.9)
13	393 (25.8)
14	654 (43.0)
15+	164 (10.8)
N of siblings	
2	597 (85.3)
3	88 (12.6)
4	11 (1.6)
5	4 (0.6)
Ethnic group	
Native American	49 (7.0)
African-American	97 (13.8)
Asian	92 (13.1)
Hispanic	155 (22.1)
White	307 (43.9)
Available sibling pairs*	
Male-male	193
Male-female	383
Female-female	205

* Because of multiple sibling pairs in some families, the total exceeds the 700 families.

Table 2 presents the results of the sibling correlations for activity hours for the full dataset as well as for different types of families. There was a statistically significant correlation for all activities between siblings regardless of sex. The overall correlations for outdoor/sports activities and diopter-hours were similar, with reading and studying correlations slightly lower. Correlations among outdoor/sports activities and family types ranged from 0.40 for brother/sister pairs to 0.77 for brother pairs.

The results of the ICC analyses are shown in Table 3. The family-level column (σ^2_f) presents the between-family variation (i.e., explaining the effects of the shared family level), while the next column presents the within-family variation (σ^2_c) explaining the unique effects at the child level. Added together these two variances estimate the total variability of refractive error. These columns allow for an assessment of how the covariates affect the two types of variability that make up the ICC ($\sigma^2_f/\ \sigma^2_c + \sigma^2_f$). The child-level variation was greater than the family-level variation for all the models presented, resulting in ICCs that were less than 0.50 for all of the models. The ICC estimate for spherical equivalent controlling for age and sex was 0.408 (95% confidence interval [CI] = 0.350, 0.470). Assuming that age and sex accounted for all environmental effects, heritability for spherical equivalent was 0.816 (0.700, 0.930). The addition of ethnicity to age and sex resulted in a noticeable decrease in the between-family variation, reducing the ICC to 0.374. The next three models sequentially add site and environmental variables to a model with age, ethnicity, and sex. As additional variables were added to the model, more of

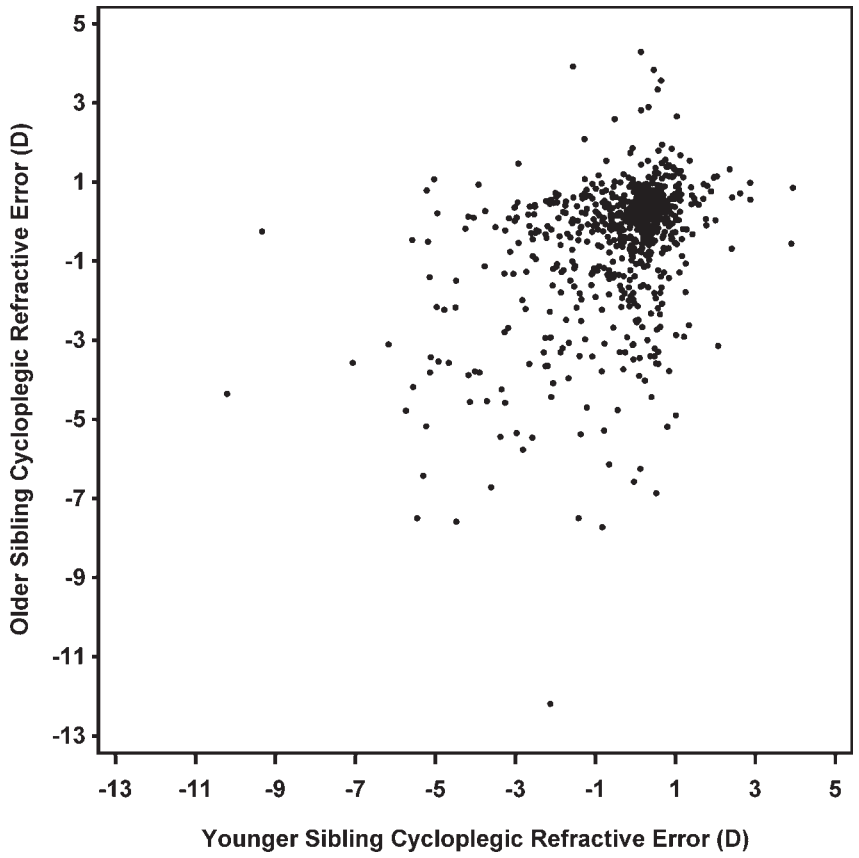

FIGURE. Correlation of refractive error between sibling pairs (or youngest and oldest sibling in the case of more than 2 siblings).

the family- and child-level variation was explained. For the model that adjusted spherical equivalent for age, sex, site, ethnicity, and outdoor/sports activity, the resulting ICC was 0.364 (0.304, 0.420). When diopter-hours per week was added, the ICC remained at 0.364 because family- and child-level variation were affected by the addition of diopter hours. The associated upper bound for heritability for this model was 0.728 (0.608, 0.850). The reduction in the ICC between the model with age, sex, site, and ethnicity, and the model that added outdoor/sports activity and diopter-hours to the environmental covariates was small. As an alternative way of examining the potential contribution of near work, the final model in Table 3 replaces diopter-hours with reading and studying hours. The resulting ICC decreases 0.2% to 0.362 with an upper bound on heritability of 0.724.

We also assessed within-sex and between-sex ICC estimates for spherical equivalent. A test of the difference between the ICC measured in female and male siblings was not statistically significant (data not shown, $P = 0.45$). We also repeated the entire analysis using only children whose age at the last study visit was at least 14 years (91 families) to restrict the analysis to the oldest sample possible. The ICC for outdoor/sports activity and diopter-hours was slightly decreased at 0.333 (0.163, 0.500), with an upper bound on heritability of 0.665. We lose all Asian families from this analysis due to lower numbers of study visits at age 14, suggesting that the original model is the more reliable and generalizable one (data not shown).

DISCUSSION

The majority of heritability estimates in vision research come from the modeling of data based on extended family information, which must attempt to parse the contribution of environmental components through assumptions. We used actual data on refractive error and some environmental exposures to complete this picture, and to calculate ICC and an upper bound for heritability based upon sibling data. Because our analysis was based upon siblings only, we do not have the variation in family structure needed to calculate the required information for the variance component models, so we approached the question using ICCs and the resulting heritability.[19,20]

The ICC and heritability estimated from sibling data after adjustment for age, sex, ethnicity, and shared and unique environmental exposures to near work and outdoor/sports activity were high (0.362 and 0.724, respectively) and very similar to most estimates in the literature. Lee et al.[21] found a similar between-sibling correlation of 0.39 in a sample where the average age was 61.5 years, in a model that did not control for environment. Likewise, the Salisbury Eye Examination study siblings had a spherical equivalent correlation of 0.31,[13] and the Beaver Dam Eye Study's siblings (mean age 71.6 years) had a spherical equivalent correlation of 0.33 after adjustment for age, sex, and education.[22] The sibling correlation in SCORM, adjusted for age and sex, was 0.447 (95% CI = 0.31, 0.56).[15] Kim et al.[23] used a dataset of twins and nontwin siblings, and found an ICC for spherical equivalent among first-degree adult sibling pairs of 0.34. When they used a variance component model, the heritability was 0.78. In contrast, Chen et al.[14] reported a sibling correlation for refractive error of 0.77 and a heritability of 0.50 using a variance components approach, suggesting a strong influence of shared environment.

While the estimate of heritability from sibling correlations agrees well with past literature, the estimate of environmental

Table 2. Within Family Correlations for Activities for Overall Dataset and by Family Type

Sibling Pair Types	Outdoor/Sports Activity h Correlation (95% CI)	Diopter-h Correlation (95% CI)	Reading h Correlation (95% CI)	Studying h Correlation (95% CI)
Full dataset	0.57 (0.52, 0.62)	0.57 (0.52, 0.62)	0.37 (0.31, 0.43)	0.49 (0.43, 0.54)
Brother/sister	0.40 (0.32, 0.49)	0.51 (0.43, 0.58)	0.30 (0.21, 0.40)	0.44 (0.36, 0.52)
Sister/sister	0.61 (0.53, 0.69)	0.61 (0.52, 0.69)	0.43 (0.32, 0.54)	0.51 (0.41, 0.61)
Brother/brother	0.77 (0.70, 0.82)	0.63 (0.55, 0.71)	0.39 (0.27, 0.50)	0.52 (0.42, 0.62)

effects does not. The effect on heritability of refractive error from shared family and unique, child-level exposure to near work and outdoor/sports activity was much lower (0.009) than previous estimates. Kim et al.[23] found no significant effect of a shared environment, but reported a significant contribution of approximately 0.16 for unique environmental effects. Others have reported model estimates for environmental effects on heritability ranging from 0.07 to 0.33.[3,4,9,14] A unique feature of the current study is the annual measurement of visual activity, allowing us to incorporate a history of prior activity levels into the analysis. Other studies used either baseline activity only, or used a traditional heritability model that assigns the environmental effects based upon model estimates; we used parent-reported data.[15]

To assume that heritability can be estimated from twice the ICC, there must be a lack of a shared environment between siblings. In theory, as we account for more environmental variables that may contribute to the development of myopia, then 2 × ICC should come closer to approaching the true heritability. Following this logic, the upper bound of the heritability, as presented in Table 3, represents the largest possible heritability; that is 0.73 (ICC = 0.364), according to our data. Based upon the high correlations for activities between siblings shown in Table 2, there appears to be a substantial shared environment in the amount of time siblings spend in different activities. The sibling correlation for refractive error in SCORM, adjusted for age and sex, was 0.447 (95% CI = 0.31, 0.56), similar to our model.[15] Their between-sibling correlation for outdoor activity was 0.52, only slightly lower than what we report for the siblings in our study, while the correlation for hours of reading was a little higher (0.603) than our diopter-hours correlation (0.570); however, that shared environment also must be effective in creating similarities in refractive error between siblings to bias the estimate of heritability. Our finding that these activities accounted for only a very small proportion in the variability of refractive error compared to the proportion accounted for by genetics suggested that individual variations in near work and time outdoors are not effective in regulating the magnitude of refractive error, wherein the spectrum of refractive error an individual lies. This is not to say that environmental effects are unimportant. Environmental effects may influence individual risk of onset[8] and population prevalence.[24] We chose two measures, time spent in near work and time in outdoors/sports activity, to represent known, important environmental influences. While it is possible that these may not represent the relevant environmental exposures, it is worth noting that Guggenheim et al.[25] collected outdoor/sports activity data similar to that gathered in CLEERE and showed that more time spent outdoors lowers the risk of the onset of myopia in children, but when they assessed the magnitude of refractive error (i.e., continuously), neither near work nor time spent outdoors had a meaningful effect. The calculation of heritability depends on correlations in refractive errors as continuous variables between siblings. It is possible, therefore, that the known effects of the environment, particularly time outdoors, on refractive error status as a categorical variable may translate into a slightly larger effect on the correlations between siblings and heritability.

An interesting finding is that the heritability between male siblings was not significantly different from that between female siblings or overall. In contrast, SCORM reported an ICC for male siblings that was no different from 0, indicating that there was no familial component to spherical equivalent in males. The female sibling correlation was on the order of 0.585, noticeably higher than the males. These correlations were only adjusted for age and sex, unlike our correlations, which accounted for environmental exposures as well.[15]

A strength of our study is the use of siblings of similar ages. Some previous publications have estimated heritability by assessing correlations in refractive error between parents and offspring.[14] This can have the effect of introducing bias from both sides. If children are assessed before their full maturation age, they may not have developed their final refractive error. Because our subjects are children rather than adults, this issue still may be a source of bias in our study. The other source of bias when using parent data is that refractive error may no longer be representative of what it was when they were younger due to the effects of age, such as a hyperopic shift.[26,27]

There also is a question of how a difference in sibling age may bias the estimate of heritability. For example, the Framingham Offspring Eye Study found that the odds ratio for the association of myopia between siblings was approximately 5.0 for a 2-year difference in siblings, while the odds

Table 3. ICC Estimates

Model	Family Level σ^2_f	Child Level σ^2_c	ICC (95% CI)	Heritability Upper Bound (95% CI)
Spherical equivalent adjusted for age and sex	1.162	1.686	0.408 (0.350, 0.470)	0.816 (0.700, 0.930)
Spherical equivalent adjusted for age, sex, ethnicity	1.008	1.689	0.374 (0.314, 0.430)	0.748 (0.627, 0.870)
Spherical equivalent adjusted for age, sex, ethnicity, and site	0.977	1.687	0.367 (0.304, 0.420)	0.733 (0.613, 0.850)
Spherical equivalent adjusted for age, sex, ethnicity, site, and outdoor/sports activity	0.965	1.685	0.364 (0.304, 0.420)	0.728 (0.608, 0.850)
Spherical equivalent adjusted for age, sex, ethnicity, site, outdoor/sports activity, and diopter-hours	0.949	1.658	0.364 (0.304, 0.420)	0.728 (0.608, 0.850)
Spherical equivalent adjusted for age, sex, ethnicity, site, outdoor/sports activity, reading, and studying	0.927	1.634	0.362 (0.302, 0.420)	0.724 (0.604, 0.840)

ratio among those siblings who were 10 years apart was approximately half of that.[28] In other words, siblings who were closer together in age were more likely to be similar in refractive error. One of the strengths of twin studies is the theoretical absolute matching on age and environment.[9] We have attempted to mediate this issue by using the last visit, optimally the eighth grade visit. As a result, the mean difference in ages between the oldest and youngest sibling in our study was only 1.24 years. We did, however, attempt more complex models that incorporated differences by age into the model and found results that were similar. Because of this, we have presented the simpler models based upon averages. Additionally, analysis restricting the sample to those siblings at least 14 years old, with a mean age difference at their last study visit of 0.5 years, found similar results in a much reduced sample.

There are several reasons for a small impact of environment, as measured by our activity data. A lack of effect may indicate that the environment has an impact at a certain time, but we may not have captured the correct time interval. It also may be that the measures we used for familial environment do not actually represent common shared effects or that they only represent a fraction of the familial environment that may have a role in determining refractive error. We estimated a family level by averaging across children and siblings within a family. Perhaps "shared" environment extends beyond the shared family level. We have attempted to adjust for these extended, shared environmental factors through adjustment for study site (i.e., school), age, and ethnicity. One of the limitations in this approach is that ethnicity may contribute to a genetic and an environmental effect.

It also is possible that environment is important, and not dependent on time, but that we do not know how to measure environment accurately. Perhaps more comprehensive assessments of activities are necessary, such as electronic monitoring, or other components (dietary, exposures, and so forty) should be addressed.[29,30]

Our results indicated that genetic contributions accounted for a large proportion of the variability in spherical equivalent in this study. Despite the presence of a correlation in environment between siblings, adjustment for this shared environment had little impact on correlation in their refractive error.

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Appendix

The Cleere Study Group (as of March, 2012)

Clinical Centers, Franklin Primary Health Center, Inc., Mobile, Alabama, United States. Sandral Hullett, MD MPH (Principal Investigator, 1997–2006), Robert N. Kleinstein, OD MPH PhD (Co-Investigator, 1997–2006), Janene Sims, OD (Optometrist, 1997–2001 and 2004–2006), Raphael Weeks, OD (Optometrist, 1999–2006), Sandra Williams (Study Coordinator, 1999–2006), LeeAndra Calvin (Study Coordinator, 1997–1999), Melvin D. Shipp, OD MPH DrPH (Co-Investigator, 1997–2004).

University of California, Berkeley School of Optometry, Berkeley, California, United States. Nina E. Friedman, OD MS (Principal Investigator, 1999–2001), Pamela Qualley, MA (Study Coordinator, 1997–2001), Donald O. Mutti, OD PhD (Principal Investigator, 1996–1999), Karla Zadnik, OD PhD (Optometrist, 1996–2001).

University of Houston College of Optometry, Houston, Texas, United States. Ruth E. Manny, OD PhD (Principal Investigator, 1997–2006), Suzanne M. Wickum, OD (Optometrist, 1999–2006), Ailene Kim, OD (Optometrist, 2003–2006), Bronwen Mathis, OD (Optometrist, 2002–2006), Mamie Batres (Study Coordinator, 2004–2006). Sally Henry (Study Coordinator, 1997–1998), Janice M. Wensveen, OD PhD (Optometrist, 1997–2001), Connie J. Crossnoe, OD (Optometrist, 1997–2003), Stephanie L. Tom, OD (Optometrist, 1999–2002), Jennifer A. McLeod (Study Coordinator, 1998–2004), Julio C. Quiralte (Study Coordinator, 1998–2005), Gaby Solis (Study Coordinator, 2005–06).

Southern California College of Optometry, Fullerton, California, United States. Susan A. Cotter, OD MS (Principal Investigator, 2004–2006, Optometrist, 1997–2004), Julie A. Yu, OD (Principal Investigator, 1997–2004; Optometrist 2005–2006), Raymond J. Chu, OD (Optometrist, 2001–2006), Carmen N. Barnhardt, OD, MS (Optometrist 2004–2006), Jessica Chang, OD (Optometrist, 2005–2006), Kristine Huang, OD (Optometrist, 2005–2006), Rebecca Bridgeford (Study Coordinator, 2005–2006), Connie Chu, OD (Optometrist, 2004–2005), Soonsi Kwon, OD (Optometrist, 1998–2004), Gen Lee (Study Coordinator, 1999–2003), John Lee, OD (Optometrist, 2000–2003), Robert J. Lee, OD (Optometrist, 1997–2001), Raymond Maeda, OD (Optometrist, 1999–2003), Rachael Emerson (Study Coordinator, 1997–1999); Tracy Leonhardt (Study Coordinator, 2003–2004).

University of Arizona, Department of Ophthalmology and Vision Science, Tucson, Arizona, United States. J. Daniel Twelker, OD PhD (Principal Investigator, 2000–2010), Mabel Crescioni, DrPh (Study Coordinator, 2009–10), Dawn Messer, OD MPH (Optometrist, 2000–2010), Denise Flores (Study Coordinator, 2000–2007), Rita Bhakta, OD (Optometrist, 2000–2004), Katie Garvey, OD (Optometrist, 2005–2008), Amanda Mendez Roberts, OD (Optometrist, 2008–2010).

Resource Centers, Chairman's Office, The Ohio State University College of Optometry, Columbus, Ohio, United States. Karla Zadnik, OD PhD (Chairman, 1997–present), Jodi M. Malone Thatcher, RN (Study Coordinator, 1997–2012).

Videophakometry Reading Center, The Ohio State University College of Optometry, Columbus, Ohio, United States. Donald O. Mutti, OD PhD (Director, 1997–present), Huan Sheng, MD PhD (Reader, 2000–2006), Holly Omlor (Reader, 2003–2006), Meliha Rahmani, MPH (Reader, 2004–2007), Jaclyn Brickman (Reader, 2002–2003), Amy Wang (Reader, 2002–2003), Philip Arner (Reader, 2002–2004), Samuel Taylor (Reader, 2002–2003), Myhanh T. Nguyen, OD MS (Reader, 1998–2001), Terry W. Walker, OD MS (Reader, 1997–2001), Vidhya Subramanian, MS (Reader, 2006–2007).

Optometry Coordinating Center, The Ohio State University College of Optometry, Columbus, Ohio, United States. Lisa A. Jones-Jordan, PhD (Director, 1997–present), Linda Barrett (Data Entry Operator, 1997–2007), John Hayes, PhD (Biostatistician, 2001–2007), G. Lynn Mitchell, MAS Biostatistician, 1998–present), Melvin L. Moeschberger, PhD (Consultant, 1997–present), Loraine Sinnott, PhD (Biostatistician, 2005–present), Pamela Wessel (Program Coordinator, 2000–present), Julie N. Swartzendruber, MA (Program Coordinator, 1998–2000), Austen Tanner (Data Entry Operator, 2008–10).

Project Office, National Eye Institute, Rockville, MD, USA: Donald F. Everett, MA

Executive Committee. Karla Zadnik, OD PhD (Chairman), Lisa A. Jones-Jordan, PhD, Robert N. Kleinstein, OD MPH PhD, Ruth E. Manny, OD PhD, Donald O. Mutti, OD PhD, J. Daniel Twelker, OD PhD, Susan A. Cotter, OD MS