Aggregation of Refractive Error and 5-Year Changes in Refractive Error Among Families in the Beaver Dam Eye Study

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Objective: To examine aggregation of refraction, myopia, hyperopia, and astigmatism, as well as the 5-year change in each of these measures, among adult family members.

Design: Geographically defined, population-based cohort study in Beaver Dam, Wis. Participants were all 43 to 84 years of age in 1988. Family relationships among participants of the study were identified through interviews. The main outcome measures were noncycloplegic refractions. Aggregation was assessed by Pearson correlations and odds ratios (ORs) that both members of a pair were affected.

Results: Age-adjusted sibling correlation of refraction was 0.37 and the OR for a sibling to be myopic was 4.18, whereas the OR for being hyperopic was 2.87 (all statistically significant, \( P < .05 \)). Correlations and ORs for parent-child and cousin relationships were smaller, and those for spousal relationships were not significant. Correlations and ORs for cylinder power and astigmatism were not statistically significant for most relationships considered. There were no statistically significant correlations or ORs for changes in any measure of refractive error.

Conclusions: The strong aggregation of refractive error, including myopia and hyperopia, among siblings along with weaker associations among parent-child and cousin pairs and no associations among spouses suggest a potential genetic influence on refractive error. There is no such suggestion for a genetic influence on the changes in refraction or in cylinder power and astigmatism.


EFFECTIVE errors are common conditions that affect vision. The contributions of environmental and genetic factors are not clearly understood. Evidence of a genetic influence on myopia is strong. Several studies have shown strong sibling correlations for refraction, whereas spouse-spouse or parent-child correlations have been low. Twin studies have found stronger correlations between monozygotic twins than dizygotic twins. Environmental influences cannot be overlooked, however. Genetic influences do not explain away environmental effects such as education, or are reduced when adjustments are made for education or similar age and presumed environment. In animals, growth of the eye can be influenced by environmental feedback. In humans, many cross-sectional studies show a higher prevalence of myopia in those with more education and with more near-work activities. There is a lack of studies on the roles of genetics and environment in hyperopia.

Refraction has been shown to change over time. The role of environmental and genetic factors on these changes is even less well understood than in cross-sectional data. Increases in myopia are found among populations with extensive near-work activities, suggesting an environmental influence on this type of refractive error in adults. Changes in refraction could also be due to other changes in the eye, such as cataract, that may have genetic components.

Familial relationships of astigmatic refractive error have been less conclusive. Some studies in twins showed more similarity of astigmatism between monozygotic twins than between dizygotic twins or between unrelated control pairs. Other studies have not found statistically significant differences in astigmatic refractive error between monozygotic and dizygotic twins.
SUBJECTS AND METHODS

Methods used to identify the population and descriptions of participants and nonparticipants appear in previous reports.\textsuperscript{24,25} Briefly, a private census of the population of Beaver Dam, Wis, was performed from fall 1987 through spring 1988. All 5924 people identified as living in Beaver Dam who were aged 43 to 84 years were eligible for participation and were invited to undergo baseline examinations from March 1988 through September 1990. All people undergoing baseline examination and surviving until March 1993 (n=4541) were invited to return for follow-up examinations from March 1993 through June 1995. A total of 3684 returned for follow-up.

Similar procedures were used at both the baseline and follow-up examinations. Tenets of the Declaration of Helsinki were followed. Informed consent was obtained from each subject, and institutional human experimentation committee approval was granted. Assessment of the refraction in the participant’s current prescription (if available) was followed by a standardized refraction using an automated refractor. The refraction was refined according to a modification of the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol\textsuperscript{26} to obtain the best-corrected visual acuity when the automated refraction yielded visual acuity of 20/40 or worse.

During the interview, participants were asked about years of education and smoking history. Education level was categorized as less than high school (<12 years completed) and high school or higher (>12 years completed). Height was measured. Photographs of the lens of each eye were taken after pharmacologic dilation, and severity of nuclear sclerosis was assessed by comparison with standard photographs, resulting in a 5-level severity scale. Mild nuclear sclerosis was defined as levels 1 and 2. Moderate nuclear sclerosis was defined by level 3, and severe nuclear sclerosis was defined by levels 4 and 5.\textsuperscript{27}

The results of the automated refraction were used in the analyses for 96% of eyes at baseline and 93% of eyes at follow-up. When the modified ETDRS refraction was performed, that refraction was used in the analyses (4% of eyes at baseline and 5% of eyes at follow-up). In the remaining people, refraction from the current prescription was used (<1% of eyes at baseline, 2% of eyes at follow-up). Eyes without a lens or with an intraocular lens were excluded because surgery alters the natural refraction of the eye. Eyes with best-corrected visual acuity of 20/40 and worse were excluded from analyses because of diminished reliability and increased variability of refractions.

The spherical equivalent (sphere power + [0.5 × positive cylinder power], all measured in diopters [D]) was calculated from the refraction. Myopia was defined as a spherical equivalent less than −0.5 D. Hyperopia was defined as a spherical equivalent greater than +0.5 D. Astigmatism was defined as cylinder power greater than +0.5 D, irrespective of axis. Incidence of myopia occurred when an eye with a spherical equivalent equal to or more positive than −0.5 D at baseline had a spherical equivalent more negative than −0.5 D at the follow-up examination. Similarly, incidence of hyperopia was defined as a change of spherical equivalent from equal to or more negative than +0.5 D at baseline to more positive than +0.5 D at follow-up. Incidence of astigmatism was defined as a change from equal to or more negative than +0.5 D of cylinder power at baseline to more positive than +0.5 D of cylinder power at follow-up (axis ignored at both baseline and follow-up).

During the baseline examination, participants were asked the names and city of residence for all of their siblings. Based on these responses, and in some cases information from obituaries, preliminary family relationships were established. During the follow-up examination phase, these family relationships were confirmed. As a final confirmation of family relationships, a follow-up telephone inquiry was made to at least 1 member of each family for participants in the Beaver Dam Eye Study with at least 1 sibling who was also eligible to participate (all calls were made by the same interviewer). A total of 1997 people participating in the baseline examination were members of 1 of 410 family groups. A family group consists of “siblings” (‘groups’ of siblings) with the same mother and father (“group” may be a single person [only child], parents, children, and spouse’s siblings [if they exist] for all members of a sibship. A sample family is shown in the Figure. We estimate that 40% of the population is in a family.

Several types of relationships were available within these family groups. For these analyses, we were interested in 4 types of relationships: sibling relationships within sibships with 2 or more members with refraction data, first cousin relationships within families where at least 2 sibships have at least 1 member of each sibship with refraction data, parent-child relationships with at least 1 parent and 1 child with refraction data, and household relationships where at least 2 members of the same household have refraction data and the members are not related.

For sibship analyses, we define a sibship to be a group of siblings where 2 or more siblings participated in the baseline examination. Among the 440 families, 290 had exactly 1 sibship, 41 had 2 sibships, 14 had 3 sibships, 5 had 4 sibships, and 12 had more than 4 sibships (2 of these families had 6 sibships) for a total of 587 sibships (1403 people) eligible for the sibling analyses. Sibships included in analyses presented herein are limited to sibling groups where 2 or more had refraction data. Thus, there were 231 families with exactly 1 qualifying sibship and 55 families with multiple qualifying sibships. Similarly, for sibling groups with 2 or more members with both baseline and follow-up refraction data, there were 174 families available with exactly 1 qualifying sibship and 28 families with multiple qualifying sibships.

In addition to sibling groups, there were also first cousin and parent-child relationships among these 440 families. A total of 149 families had at least 1 first cousin relationship. Of these, 138 families had first cousin relationships with refraction data for all relevant subjects. Similarly, 130 families had sibships with a parent in the study, and 100 other relationships were available in these family groups.

In an attempt to understand the potential influence of genetic factors on changes in refraction, we describe correlations between family members for refractive errors and changes in them among members of the Beaver Dam Eye Study population.

RESULTS

Comparisons of age, sex, education, height, smoking, and nuclear cataract status for the entire Beaver Dam popu-
of these had refraction data for both the children and at least 1 parent. We also had 1292 households that contained at least 2 members with refraction data.

Several of our families (72 of the 440) contained multiple sibships, which could be directly related (as first cousins or as avuncular [aunt/uncle-niece/nephew] relationships). For each type of relationship examined, we restricted our analyses to independent groups so standard statistical software would provide valid results. To achieve independence, exclusions were made for families with multiple qualifying relationships. Within each family, all qualifying relationships were identified (for example, in sib-sib analyses, a qualified relationship is a sibship with 2 or more members with refraction data). From the list of qualified relationships, 1 was selected at random. All direct relatives of this group were excluded. Another qualifying relationship was randomly selected from the remaining groups and direct relatives were excluded. This was continued until no groups remained. This method allowed us to use information from these complex families while maintaining independence. We did the analyses 100 times using different randomly selected groups and found the qualitative conclusions did not appear to be affected by the random selection process.

For example, consider the pedigree in the Figure. Sibling groups are identified by a number along the bar connecting the siblings. For sibship analyses, sibships 4, 5, 8, 10, 11, 12, 13, 14, and 15 all potentially qualify for analyses, while sibships 6 and 9 do not qualify because they are only children and sibships 1, 2, 3, and 7 do not qualify because they do not have enough participating siblings. We randomly choose sibship 5. Sibship 4 was excluded because the sibs are cousins. Sibship 15 was then randomly selected and sibships 10 (parent and uncle) and 14 (first cousins) were excluded. Sibship 11 was randomly selected. There were no exclusions from relationships to sibship 11. Sibship 8 was randomly selected, which also leads to no further exclusions since sibship 10 (cousin) was already excluded. Finally, sibship 12 was selected, which caused sibship 13 to be excluded (first cousin), and no other sibships were available for selection.

Similar approaches were taken for first cousin, parent-child, and household relationships. Consider again the Figure for cousin analysis; sibships 4, 5, and 6 are group 1; sibships 6 and 7 are group 2; sibships 7, 8, 9, and 10 are group 3; sibships 12 and 13 are group 4; and sibships 14 and 15 are group 5. We randomly selected group 4, so sibship 7 was eliminated (since these sibs are the parents of a member of the group). By eliminating sibship 7, we effectively eliminated group 2 from analyses. Next we randomly selected group 1, which did not cause any other exclusions. Then we selected group 5, which caused sibship 10 to be excluded. This did not have any effect, however. Finally, group 3 was selected (even though sibships 7 and 10 were not included in the analyses). A similar example could be constructed for the parent-child and household groups.

SAS statistical software (SAS Institute Inc, Cary, NC) was used for analyses. Aggregation of dichotomous outcomes (myopia, hyperopia, astigmatism, incidence of myopia, incidence of hyperopia, and incidence of astigmatism) was assessed by looking at odds ratios (ORs) performed using second-order generalized estimating equations (GEE2) for both interclass and intraclass associations. Intraclass correlations are done when both members of the pair are part of the same class (sib-sib, spouse-spouse, sister-sister). Interclass correlations are done when the members of the pair are from different classes (parent-child, cousin-cousin, brother-sister). Because of the size limitations of the program, we had to exclude groups with more than 8 members (this only occurred for cousin analyses). The OR is the odds of a person being affected given the other person in the pair is affected vs the other person in the pair is not affected. In other words, the OR for persons j and k in a pair can be defined by the following:

$$ OR_{jk} = \frac{Pr(Y_j = 1, Y_k = 1) / Pr(Y_j = 0, Y_k = 0)}{Pr(Y_j = 0, Y_k = 0) / Pr(Y_j = 1, Y_k = 1)} $$

where Pr indicates probability, $Y_j$ when person j is affected; and $Y_k$ when person k is unaffected.

Although the GEE2 modeling procedure allows for adjustments to ORs, we only adjusted for age (using 5-year age groups, unless otherwise noted) for the marginal estimates of the risk that a person is affected [$Pr(Y_j=1)/Pr(Y_j=0)$]. Adjustment for sex and education was done when there were adequate group sizes and results did not change, so this is not presented.

Correlation of continuous outcomes (refraction, change in refraction, cylinder power, and change in cylinder power) was calculated using Pearson correlation among all possible pairs for intraclass associations and among ordered pairs for interclass correlations. Age adjustment was carried out by standardizing the outcome within age groups (subtract the population mean and divide by the SD). Confidence intervals (CIs) were calculated using the Fisher z transformation (FZ):

$$ FZ(corr) = \frac{1}{2} \log \left( \frac{1 + corr}{1 - corr} \right) $$

The 95% CI around FZ(corr) is

$$ FZ(corr) \pm 1.96 \sqrt{\frac{1}{D - 3}} $$

where D is the effective sample size over all families.

$$ D = \sum_{i=1}^{N} \frac{a_i b_i}{[(1 + (a_i - 1)corr_{ij})[1 + (b_i - 1)corr_{ij}]]} $$

where $a_i$ and $b_i$ represent the number of people in class a and class b, with their corresponding correlations (for intraclass correlations, $a=b$). The CI around the correlation is the inverse Z transformation: [$e^{2FZ(corr)} - 1]/[1 + e^{2FZ(corr)} + 1]$. This method gives more weight to larger families, but is not a concern in this analysis since most of our sibships were similar in size (278 sibships with 2 siblings, 72 with 3 siblings, 20 with 4 siblings, 5 with 5 siblings, and 3 with 6 siblings).

Table 1: SAS statistical software (SAS Institute Inc, Cary, NC) was used for analyses. Aggregation of dichotomous outcomes (myopia, hyperopia, astigmatism, incidence of myopia, incidence of hyperopia, and incidence of astigmatism) was assessed by looking at odds ratios (ORs) performed using second-order generalized estimating equations (GEE2) for both interclass and intraclass associations. Intraclass correlations are done when both members of the pair are part of the same class (sib-sib, spouse-spouse, sister-sister). Interclass correlations are done when the members of the pair are from different classes (parent-child, cousin-cousin, brother-sister). Because of the size limitations of the program, we had to exclude groups with more than 8 members (this only occurred for cousin analyses). The OR is the odds of a person being affected given the other person in the pair is affected vs the other person in the pair is not affected. In other words, the OR for persons j and k in a pair can be defined by the following:

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$$ D = \sum_{i=1}^{N} \frac{a_i b_i}{[(1 + (a_i - 1)corr_{ij})[1 + (b_i - 1)corr_{ij}]]} $$

where $a_i$ and $b_i$ represent the number of people in class a and class b, with their corresponding correlations (for intraclass correlations, $a=b$). The CI around the correlation is the inverse Z transformation: [$e^{2FZ(corr)} - 1]/[1 + e^{2FZ(corr)} + 1]$. This method gives more weight to larger families, but is not a concern in this analysis since most of our sibships were similar in size (278 sibships with 2 siblings, 72 with 3 siblings, 20 with 4 siblings, 5 with 5 siblings, and 3 with 6 siblings).
The results for family analyses of baseline refractive error, myopia, and hyperopia indicate a strong sibling relationship for all 3 end points (Table 2). Correlation of refraction between siblings is 0.37 (95% CI, 0.31-0.42). The odds of a sibling being myopic given the other sibling is myopic vs the other sibling is not myopic is 4.18 (95% CI, 2.64-6.62). Similarly, the odds of being hyperopic given the other sibling is hyperopic is 2.87 (95% CI, 1.92-4.28). Similar but smaller correlations and ORs (sometimes nonsignificant) exist for parent-child and cousin relationships. There does not appear to be any household (assumed to be spousal) relationship.

These results are based on a random selection of sibships from the entire population, as described in the “Subjects and Methods” section. To determine if these results may reflect a selection of extreme families, we reran these analyses 100 times with different random selections of sibships each time. From these 100 analyses, we found that the sibling correlation of refraction ranged from 0.33 to 0.39. The mean and median were both 0.36 and the SD was 0.01. All the correlations were significant (P<.001). Similarly, the ORs for myopia and hyperopia remained significant for all 100 runs. The OR for myopia ranged from 2.82 (95% CI, 1.80-4.41) to 4.25 (95% CI, 2.69-6.72). The average OR was 3.42 (SD, 0.27) and the median OR was 3.37. The correlation would be significant on either the high or low end of the range. Similarly, the OR for hyperopia ranged from 2.19 (95% CI, 1.51-3.19) to 3.16 (95% CI, 2.11-4.74). The average OR was 2.74 (SD, 0.19) and the median OR was 2.72. The observed OR is close to this mean value.

There was a modest correlation of cylinder power among siblings (correlation, 0.13; 95% CI, 0.07-0.20) and cousins (correlation, 0.10; 95% CI, 0.01-0.10) (Table 3). This is not true for astigmatism, however. There does not appear to be any relationship between cylinder power or astigmatism for parent-child pairs or household pairs.

The ORs for myopia, hyperopia, and astigmatism are similar for brother-brother, sister-sister, and brother-sister relationships (Table 4) and follow the same trends observed for the sibling relationships in Tables 2 and 3. For myopia and hyperopia, the sister-sister ORs are highest (4.64 and 3.16, respectively) and the brother-brother ORs are lowest (3.36 and 2.47, respectively). For astigmatism, the opposite is true; brother-brother ORs are highest (1.32) and sister-sister ORs are lowest (0.72). None of the ORs for astigmatism reach statistical significance.

Table 1. Distribution of Baseline Risk Factors for Subpopulations in Analyses

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Whole Population (N = 4926)</th>
<th>Families (n = 1997)</th>
<th>Sibling Analyses (n = 895)</th>
<th>Cousin Analyses</th>
<th>Parent-Child Analyses</th>
<th>Household Analyses (n = 1728)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>62.0 (11.2)</td>
<td>63.0 (10.8)</td>
<td>61.5 (9.5)</td>
<td>61.9 (9.3)</td>
<td>61.6 (9.8)</td>
<td>74.3 (5.0)</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>56.1</td>
<td>54.2</td>
<td>50.3</td>
<td>50.2</td>
<td>51.1</td>
<td>68.5</td>
</tr>
<tr>
<td>Education, % graduated high school or higher</td>
<td>70.7</td>
<td>63.6</td>
<td>64.7</td>
<td>69.5</td>
<td>68.6</td>
<td>31.5</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>166.1 (9.4)</td>
<td>165.6 (9.4)</td>
<td>166.6 (9.1)</td>
<td>166.6 (9.1)</td>
<td>167.1 (9.1)</td>
<td>161.5 (7.6)</td>
</tr>
<tr>
<td>Smoking, %</td>
<td></td>
<td>35.5</td>
<td>35.5</td>
<td>40.5</td>
<td>34.1</td>
<td>25.9</td>
</tr>
<tr>
<td>Past</td>
<td>19.7</td>
<td>17.7</td>
<td>19.7</td>
<td>18.6</td>
<td>18.5</td>
<td>7.4</td>
</tr>
<tr>
<td>Current</td>
<td></td>
<td></td>
<td></td>
<td>35.5</td>
<td>36.3</td>
<td>44.7</td>
</tr>
<tr>
<td>Nuclear sclerosis, %</td>
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<td>35.5</td>
<td>44.7</td>
</tr>
<tr>
<td>Moderate (level 3)</td>
<td></td>
<td></td>
<td></td>
<td>32.3</td>
<td>34.9</td>
<td>44.7</td>
</tr>
<tr>
<td>Severe (level 4 or 5)</td>
<td></td>
<td>13.1</td>
<td>14.3</td>
<td>10.1</td>
<td>12.0</td>
<td>8.8</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Sample family diagram. Circles indicate females; squares, males; and solid circles or squares, participating individuals.
Changes in spherical equivalent, incident myopia, and incident hyperopia (Table 5) and changes in cylinder power and incident astigmatism (Table 6) in the 5-year interval show no important associations of change or incidence by any of the family relationships examined. Incidence of myopia is rare in this population (4.2%), and we do not have any pairs of family members where both are affected, so ORs were not calculated. Similarly, incidence of hyperopia is rare (14.4%), and when ORs are calculated, the CI is wide. Although the OR for siblings for incident hyperopia is significant, it is not a strong relationship. Changes and incidence among households are not significant either.

Refraction is strongly related among siblings. The age-adjusted correlation of 0.37 (unadjusted correlation, 0.41; data not shown) is similar to correlations observed in other studies. Bear et al. found age- and sex-adjusted sib-sib correlations of 0.39 in the 76 sibships older than 30 years. They also found that sister-sister correlations were slightly higher than brother-brother correlations. This is consistent with our findings. In contrast, Alsbirk observed a sib-sib correlation of 0.25, with brother-brother correlations slightly higher than sister-sister correlations. The

Table 2. Familial Relationships of Spherical Equivalent, Myopia, and Hyperopia

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Spherical Equivalent</th>
<th>Myopia</th>
<th>Hyperopia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Pairs</td>
<td>Correlation (95% CI)</td>
<td>No. of Pairs</td>
</tr>
<tr>
<td>Sibling</td>
<td>1418</td>
<td>0.37 (0.31 to 0.42)</td>
<td>709</td>
</tr>
<tr>
<td>Spouse</td>
<td>1740</td>
<td>0.01 (-0.03 to 0.06)</td>
<td>870</td>
</tr>
<tr>
<td>Parent-child</td>
<td>225</td>
<td>0.29 (0.15 to 0.42)</td>
<td>225</td>
</tr>
<tr>
<td>Cousin</td>
<td>607</td>
<td>0.17 (0.05 to 0.28)</td>
<td>607</td>
</tr>
</tbody>
</table>

*OR indicates odds ratio; CI, confidence interval.

Table 3. Familial Relationships of Cylinder Power and Astigmatism

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Cylinder Power</th>
<th>Astigmatism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Pairs</td>
<td>Correlation (95% CI)</td>
</tr>
<tr>
<td>Sibling</td>
<td>1418</td>
<td>0.13 (0.07 to 0.20)</td>
</tr>
<tr>
<td>Spouse</td>
<td>1740</td>
<td>-0.02 (-0.07 to 0.03)</td>
</tr>
<tr>
<td>Parent-child</td>
<td>225</td>
<td>-0.01 (-0.15 to 0.12)</td>
</tr>
<tr>
<td>Cousin</td>
<td>607</td>
<td>0.10 (0.01 to 0.19)</td>
</tr>
</tbody>
</table>

*OR indicates odds ratio; CI, confidence interval.

Table 4. Sibling Relationships of Myopia, Hyperopia, and Astigmatism by Sex

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Myopia</th>
<th>Hyperopia</th>
<th>Astigmatism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Pairs</td>
<td>OR (95% CI)</td>
<td>No. of Pairs</td>
</tr>
<tr>
<td>Brother-brother</td>
<td>188</td>
<td>3.36 (1.56 to 7.21)</td>
<td>188</td>
</tr>
<tr>
<td>Sister-sister</td>
<td>189</td>
<td>4.64 (1.91 to 11.28)</td>
<td>189</td>
</tr>
<tr>
<td>Brother-sister</td>
<td>332</td>
<td>4.32 (2.44 to 8.37)</td>
<td>332</td>
</tr>
</tbody>
</table>

*OR indicates odds ratio; CI, confidence interval.

Table 5. Familial Relationships of Changes in Spherical Equivalent, Incident Myopia, and Incident Hyperopia

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Change in Spherical Equivalent</th>
<th>Incident Myopia</th>
<th>Incident Hyperopia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Pairs</td>
<td>Correlation (95% CI)</td>
<td>No. of Pairs</td>
</tr>
<tr>
<td>Sibling</td>
<td>760</td>
<td>0.01 (-0.08 to 0.09)</td>
<td>231</td>
</tr>
<tr>
<td>Spouse</td>
<td>1098</td>
<td>-0.06 (-0.12 to 0.00)</td>
<td>250</td>
</tr>
<tr>
<td>Parent-child</td>
<td>96</td>
<td>0.00 (-0.20 to 0.20)</td>
<td>63</td>
</tr>
<tr>
<td>Cousin</td>
<td>325</td>
<td>-0.03 (-0.14 to 0.09)</td>
<td>201</td>
</tr>
</tbody>
</table>

*OR indicates odds ratio; CI, confidence interval; and ellipses, no pair with both affected, so unable to calculate odds ratio.
strong OR observed in the Beaver Dam population of 4.18 for myopia in siblings corresponds to observations reported in the Framingham Offspring Eye Study in which ORs ranged from 2.50 among siblings with 10 years' difference between the oldest and youngest to 5.13 in siblings with 2 years' difference in age. We are unaware of studies other than ours evaluating risk of hyperopia among siblings that compare with our OR of 2.87.

Refraction, myopia, and hyperopia are not significantly related in spouses. This is consistent with other studies. We found the correlation among people living in the same household (assumed to be spouses) was 0.01 after adjusting for age (unadjusted correlation, 0.11; borderline significance [95% CI, 0.07-0.16]; data not shown). No correlation between parents was found in either the study by Bear et al or the study by Alsbirk. Support the notion that cylinder power and astigmatism do not aggregate in families. This is consistent with the data from twin studies.

The relationship between refractions for parents and children reported herein is similar in magnitude to that reported in other studies. We found parent-child correlations of 0.29 after adjusting for age (unadjusted correlation, 0.31; data not shown). Bear et al found parent-child correlations ranging from 0.10 to 0.33, and Alsbirk found correlations of 0.07.

We found a modest relationship of refraction among cousins of 0.17 after adjustment for age. The OR for myopia was not significant, whereas the OR for hyperopia was of borderline significance. We are unaware of other reports of cousin correlations. Under a genetic model, we would expect sibling and parent-child correlations to be the same and cousin correlations to be smaller. The finding that the cousin correlation is nearly half the sibling correlations is compatible with a genetic influence.

The finding that the parent-child correlation is smaller than the sibling correlation suggests a possible environmental influence on refractive error. Under a genetic model, we would expect similar correlations for siblings and for parents and children. Since siblings tend to share a more common environment than parents and children, this could explain the increased correlation we observed among siblings. The primary hypothesized environmental influence is education and amount of near work. We know that education also aggregates in families in our population. Adjustment for education in all analyses did not affect results. This is likely due to the strong aggregation of education in families. Because of small numbers, we were only able to adjust for education in 2 categories (less than high school and high school or higher), which may not be adequate. The finding that education level is more similar in siblings than in parents and siblings could explain the increased correlation observed in siblings. However, we would expect the education level to be similar among cousins, so the correlation for cousins should be close to that in siblings. Since the cousin correlation was lower than the sibling correlation, as would be supported by a genetic model, we believe both environmental and genetic components of refractive error are being observed.

We have found a modest aggregation of cylinder power but not of astigmatism (defined as a categorical cut point of cylinder power >0.5 D) in siblings and among cousins. The lack of findings for astigmatism may reflect the arbitrary cut point (>0.5 D) imposed. Our data support the notion that cylinder power and astigmatism do not aggregate in families. This is consistent with the data from twin studies.

Family relationships do not seem to influence changes in refraction, either spherical equivalent or cylinder power. To our knowledge, this is the first study to evaluate changes in refractive error in families. The number of people eligible for analyses becomes rather small in this population, possibly affecting our ability to detect relationships. The lack of relationships is not unexpected because it is believed that the environment plays the biggest role in changes in refractive error in adults. Although severity of nuclear sclerosis plays an important role in the amount of change in refractive error in adults, it is unclear what genetic components may exist for cataract and how they would affect our analyses.

In summary, we have found a strong sibling association of refractive error, including myopia and hyperopia. Parent-child and cousin associations were also significant, but not as strong. Associations among unrelated household members did not exist. A modest association of cylinder power existed for sibling and cousin groups, but not for parent-child or household relations. The association for astigmatism failed to reach statistical significance in any of the family groups. No associations for 5-year changes in any of the types of refractive error were found to be significant for any of the types of family relationships. Although we cannot quantitate the relative contribution of environmental effects, these results are still suggestive of a genetic component of refractive error.

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Table 6. Familial Relationships of Change in Cylinder Power and Incident Astigmatism

<table>
<thead>
<tr>
<th>Relationship</th>
<th>No. of Pairs</th>
<th>Correlation (95% CI)</th>
<th>No. of Pairs</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibling</td>
<td>760</td>
<td>-0.04 (-0.13 to 0.04)</td>
<td>88</td>
<td>0.39 (0.18 to 0.85)</td>
</tr>
<tr>
<td>Spouse</td>
<td>1098</td>
<td>0.04 (-0.02 to 0.10)</td>
<td>135</td>
<td>0.36 (0.13 to 1.00)</td>
</tr>
<tr>
<td>Parent-child</td>
<td>96</td>
<td>0.00 (-0.20 to 0.20)</td>
<td>20</td>
<td>. . .</td>
</tr>
<tr>
<td>Cousin</td>
<td>336</td>
<td>0.04 (-0.06 to 0.14)</td>
<td>81</td>
<td>1.40 (0.53 to 3.71)</td>
</tr>
</tbody>
</table>

*OR indicates odds ratio; CI, confidence interval; and ellipses, no pair with both affected, so unable to calculate odds ratio.
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