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Correlations in refractive errors between siblings in the Singapore Cohort Study of Risk factors for Myopia

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Background: The prevalence of myopia in parts of South East Asia has risen dramatically over the past 1–2 generations, suggesting that environmental factors may be particularly important determinants of refractive development in these populations.

Aim: To assess the contribution of familial factors (shared genes and/or shared family environment) to refractive error and ocular component dimensions of school-aged children in Singapore.

Methods: Data were available for 315 children who had one or more siblings also participating in the Singapore Cohort Study of the Risk factors for Myopia (SCORM). Refractive error and ocular biometric parameters were measured under cycloplegia at baseline when children were 7–9 years, and at yearly follow-up sessions for the next 3 years, using consistent clinical procedures. The time children spent performing a variety of nearwork-related tasks was obtained from questionnaires. Familial influences were assessed by calculating between-sibling correlations.

Results: After adjusting for age and sex, the between-sibling correlation in refractive error was 0.447 (95% CI 0.314 to 0.564), suggesting that familial factors account for 63–100% of the variation in the cohort. The between-sibling correlation for 1-year change in refractive error was similarly high, at 0.420 (95% CI 0.282 to 0.543). All ocular component dimensions were correlated significantly between siblings, especially for corneal curvature and vitreous chamber depth—the major structural determinants of refraction. The amount of time siblings spent engaged in nearwork tasks (reading, watching TV, playing video games, computing) and in outdoor activities was also highly correlated between siblings (p<0.001).

Conclusion: Shared genes and/or shared environment are important factors in the refractive development of children in Singapore. Because the time spent in nearwork tasks is highly correlated between siblings, epidemiological studies will benefit from precise, quantitative measures of refractive error in parents and more distant relatives in order to begin to dissociate genetic and environmental sources of variation.

Methods
Study population and clinical procedures
All children aged 7–9 years at baseline attending three schools in Singapore were invited to participate in the SCORM. Children with syndromic myopia, congenital cataract, serious systemic diseases or who refused instillation of eyedrops were excluded. Written informed consent was obtained after the nature of the study had been explained to parents. The study received approval from the Singapore Eye Research Institute Ethics Committee, and followed the tenets of the Declaration of Helsinki for research involving human subjects. Details of the study have been reported previously.

Longitudinal studies offer a powerful approach to examine risk factors for myopia. One such longitudinal study, the Singapore Cohort Study of the Risk factors for Myopia (SCORM) is following the refractive development of a large sample of children attending three schools in Singapore. We assessed the familial contribution to (1) refractive error; (2) the change in refractive error during a 1-year period; (3) ocular component dimensions; and (4) 1-year change in ocular component dimensions, for pairs of siblings participating in the SCORM. We also investigated the extent to which children’s nearwork and outdoor activity habits were correlated, in order to explore whether these environmental factors were likely to have contributed to the resemblance between siblings.
spent watching TV, playing video games, using a computer, reading and the number of hours per week playing outdoors.

Three hundred and fifteen children had one or more siblings also participating in the study. We removed the two known pairs of twins, as well as three siblings from a sibship in which two siblings shared the same age (potential twins). This left 306 subjects for analysis, including 4 families each with 3 participating siblings. These 3-sibling families each permitted 3 sets of pairwise sibling comparisons, giving a total of 159 possible pairwise comparisons for the final dataset. The ethnic distribution of the 159 pairs of siblings was Chinese, 98 pairs (62%); Malay, 53 pairs (33%); and Indian, 8 pairs (5%). In the experience of SMS, it is very unlikely that siblings in Singapore live in different households. The mean (SD) age difference between siblings was 1.4 (0.6) years.

**Trait magnitude data analysis**

We analysed data for each subject’s most recent visit, under the assumption that this would represent the best available indicator of the subject’s refractive error and eye size in adulthood. The subject’s age at the latest visit was coded separately for each trait being considered. All ocular component dimensions had a normal frequency distribution, whereas the distribution of MSE was leptokurtotic and skewed towards myopia (Kolmogorov–Smirnov test; p<0.001). Since arithmetic transformations did not remove the non-normality, a ranking-based method of transformation was used.\(^{17}\) Linear regression and correlation analyses were carried out using SPSS V.12. As Pearson and Spearman correlations were similar (for these and subsequent analyses), only the Spearman correlations are reported in the Results section.

Odds ratios (ORs) were calculated in the 147 sibships containing 2 siblings. For these calculations, myopia, moderate myopia and high myopia were classified as untransformed refractive errors (MSE) in the right eye at the latest visit of \(\leq -0.50\), \(\leq -3.00\) and \(\leq -6.00\), respectively.

**Change in trait magnitude data analysis**

Each subject’s 1-year change in trait value was averaged across all available years and then adjusted for the effects of age and sex using linear regression. Statistical outliers were detected and removed before averaging. The frequency distributions of the 1-year changes were all non-normal, except for axial length. However, unlike with MSE, simple log or power functions were sufficient to transform the data to normality (not shown). Between-sibling correlations were calculated as described above.

**RESULTS**

**Refractive error and ocular component dimensions**

There were 159 sibling pairs in the SCORM cohort available for analysis after the removal of twins, and using all 3 potential pairwise comparisons for sibships comprising 3 siblings. After adjusting for age and sex using linear regression, there were significant between-sibling correlations in the magnitude of all the traits investigated (table 1). Refractive error, corneal curvature and vitreous chamber depth were the most highly correlated traits, suggesting that familial factors are important determinants for these traits. Anterior chamber depth seemed to be the least familial trait.

In the 147 sibships containing 2 siblings, the OR for myopia was 3.24 (95% CI 1.61 to 6.52; \(p<0.001\)), and the OR was 2.90 (95% CI 1.31 to 6.44; \(p<0.01\)) for moderate myopia. Too few children were highly myopic to provide a reliable estimate of the OR for high myopia (OR 11.50, 95% CI 0.91 to 145.20).

**One-year changes in refractive error and ocular component dimensions**

The average yearly changes in refractive error and ocular component dimensions were calculated for each sibling in the SCORM cohort, and then adjusted for the effects of age and sex. Table 2 shows sibling correlations for these 1-year changes in trait magnitude. There was strong evidence for a familial contribution to the changes in refractive error and vitreous chamber depth.

**Exposure to environmental risk factors**

As table 3 shows, the time spent engaging in each of the nearwork-related activities examined was significantly correlated between siblings. This was also true of the time children spent playing outdoors.

**DISCUSSION**

Familial factors gave rise to a highly significant similarity between siblings for refractive error: the correlation in MSE suggests that familial factors account for 63–100% of the variation of refractive error in this population (as estimated from twice the 95% CI for transformed MSE). Interestingly,
rates of refractive progression were also highly correlated between siblings, consistent with the above conclusion. Again, this could be due to similar genetic susceptibility, similar lifestyle behaviours or a combination of the two.

If siblings do not share similar levels of exposure to environmental risk factors for myopia, then one can conclude that familial resemblance must be wholly genetic in origin. Under these circumstances, and if one further assumes that all genetic variation is the result of additive polygenes, then the heritability of refractive error can be calculated as twice the correlation between siblings (which would give a heritability of about 0.90 for children in the SCORM). However, our results show that the assumption that siblings do not share similar levels of exposure to risk factors for myopia is probably wrong. Exposure to all the putative risk factors studied here was highly correlated between siblings. Thus, for siblings participating in the SCORM, it is not possible to unravel the influence of shared genes and shared environment.

Few studies have reported sibling–sibling correlations for refractive error. In the study by Young et al., the brother–brother correlation for refractive error (r = 0.32) was lower than the sister–sister correlation (r = 0.72), with the brother–sister correlation being intermediate (r = 0.45). A similar pattern was evident for the children in the SCORM (table 4).

However, the sex differences observed here were not statistically significant.

Conclusions
Precise distinctions between genetic and environmental sources of variation are inevitably artificial and can be difficult to interpret. Perhaps more important is that risk factors for myopia are discovered at all, rather than whether they are subsequently deemed to be genetic or environmental in origin, and genetic versus environment distinctions may be helpful to this end. Between 63% and 100% of the variance in refractive error of children in the SCORM can be explained by familial factors. However, our results suggest that epidemiological data collected from siblings alone do not permit the partitioning of the observed variation in refractive error into genetic and environmental sources. Thus, the collection of quantitative measures of refractive error in parents and more distant relatives, or detailed molecular genetic analysis of children in the study cohort, may be valuable strategies in the future.

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Table 3  Correlations between siblings for engagement in nearwork tasks

<table>
<thead>
<tr>
<th>Task</th>
<th>Correlation</th>
<th>95% CI</th>
<th>Significance (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reading (h)</td>
<td>0.603</td>
<td>0.494 to 0.695</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Books per week</td>
<td>0.443</td>
<td>0.310 to 0.561</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Outdoor activity (h)</td>
<td>0.517</td>
<td>0.387 to 0.629</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TV (h)</td>
<td>0.576</td>
<td>0.463 to 0.672</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Video games (h)</td>
<td>0.555</td>
<td>0.437 to 0.656</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Computing (h)</td>
<td>0.641</td>
<td>0.540 to 0.726</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 4  Correlations between same-sex and brother–sister sibling pairs

<table>
<thead>
<tr>
<th>Measure</th>
<th>Correlation</th>
<th>95% CI</th>
<th>Significance (p value)</th>
<th>n†</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSE*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brother–brother</td>
<td>0.029</td>
<td>−0.317 to 0.369</td>
<td>0.873</td>
<td>33</td>
</tr>
<tr>
<td>Brother–sister</td>
<td>0.546</td>
<td>0.392 to 0.673</td>
<td>&lt;0.001</td>
<td>98</td>
</tr>
<tr>
<td>Sister–sister</td>
<td>0.585</td>
<td>0.281 to 0.791</td>
<td>0.001</td>
<td>28</td>
</tr>
<tr>
<td>Corneal curvature</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brother–brother</td>
<td>0.272</td>
<td>−0.074 to 0.566</td>
<td>0.120</td>
<td>33</td>
</tr>
<tr>
<td>Brother–sister</td>
<td>0.474</td>
<td>0.306 to 0.616</td>
<td>&lt;0.001</td>
<td>98</td>
</tr>
<tr>
<td>Sister–sister</td>
<td>0.501</td>
<td>0.166 to 0.741</td>
<td>0.007</td>
<td>28</td>
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<tr>
<td>Vitreous chamber depth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brother–brother</td>
<td>0.144</td>
<td>−0.213 to 0.471</td>
<td>0.429</td>
<td>32</td>
</tr>
<tr>
<td>Brother–sister</td>
<td>0.412</td>
<td>0.234 to 0.566</td>
<td>&lt;0.001</td>
<td>97</td>
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<tr>
<td>Sister–sister</td>
<td>0.666</td>
<td>0.400 to 0.836</td>
<td>&lt;0.001</td>
<td>28</td>
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<tr>
<td>Change in MSE*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brother–brother</td>
<td>0.398</td>
<td>0.070 to 0.656</td>
<td>0.038</td>
<td>33</td>
</tr>
<tr>
<td>Brother–sister</td>
<td>0.412</td>
<td>0.229 to 0.566</td>
<td>&lt;0.001</td>
<td>95</td>
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<tr>
<td>Sister–sister</td>
<td>0.542</td>
<td>0.214 to 0.769</td>
<td>0.003</td>
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<tr>
<td>Change in vitreous chamber depth*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brother–brother</td>
<td>0.247</td>
<td>−0.114 to 0.556</td>
<td>0.193</td>
<td>31</td>
</tr>
<tr>
<td>Brother–sister</td>
<td>0.269</td>
<td>0.072 to 0.448</td>
<td>0.010</td>
<td>94</td>
</tr>
<tr>
<td>Sister–sister</td>
<td>0.609</td>
<td>0.309 to 0.807</td>
<td>0.001</td>
<td>27</td>
</tr>
</tbody>
</table>

MSE, mean spherical equivalent.
All measures are for the right eye only, and are adjusted for the effects of age and sex.
*Values were transformed to normality before regression and correlation calculations.
†Number of sibling pairs.
REFERENCES


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