

# Estimating Heritability and Shared Environmental Effects for Refractive Error in Twin and Family Studies

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**PURPOSE.** Twin studies have demonstrated a high heritability for refractive error of up to 90%, but some family studies have suggested up to one-third of population variance is attributable to the effects of shared family environment. This large twin study aimed to explore the role of shared environment in refractive error.

**METHODS.** Refractive error was measured using autorefractometry in 4602 subjects (1152 monozygotic and 1149 dizygotic twin pairs), aged between 16 and 82 years, recruited from the TwinsUK Adult Twin Registry. Maximum-likelihood methods were used to estimate the variance of genetic, environmental, and age variance components.

**RESULTS.** Maximum likelihood model fitting estimate of the heritability from the best-fit model was 77% (95% confidence interval [CI], 68%–84%). Shared environmental effects explained 7% (95% CI, 0%–15%) and individual environmental effects explained 16% (95% CI, 15%–18%) of the spherical equivalent variance, respectively. Inclusion of age effects into the modeling reduced shared environmental effects to an estimated 2% of variation.

**CONCLUSIONS.** Analysis of 2301 twin pairs confirms that the twin study design results in a very low estimate of shared family environmental effects in refractive error. Several factors may explain these differences; we believe the most likely is that twins are perfectly age matched and do not include cross-generation or cohort effects. This means twin study designs have more power to detect heritable effects in variance component models of myopia, whereas family studies have more power to detect shared environment effects. (*Invest Ophthalmol Vis Sci.* 2009;50:126–131) DOI:10.1167/iovs.08-2385

Refractive error is the most common eye disease and is one of the priority targets of World Health Organization Vision 2020.<sup>1</sup> Myopia affects approximately one-third of adults older than 20 years in the United States,<sup>2</sup> and areas with high prevalence,

specifically in urban East Asia, where more than 80% of students finishing school are myopic,<sup>3,4</sup> suggest an important role for environmental factors in its etiology. Myopia is now the commonest cause of blindness in working age populations in some countries.<sup>1</sup> Myopia is defined as a state of refraction wherein parallel rays of light focus in front of the retina in the unaccommodated eye, causing a blurred image, and it is measured by spherical equivalent (SphE) in diopters (D). Its development is associated with structural changes of the eye; myopic eyes have longer axial lengths, larger vitreous chambers, deeper anterior chambers, and thinner lenses than nonmyopic eyes.<sup>5,6</sup> Age of onset is usually in childhood, and progression continues until late adolescence or older. Myopia prevalence tends to decline with age in adults from approximately age 30<sup>7–12</sup> and increases again in very elderly people (because of cataract-induced myopia).<sup>2,13</sup>

Refractive error is a complex trait influenced by numerous genetic and environmental factors. The relative importance of genes and environment influencing individual variation can be estimated from family studies. One of the pioneering family studies, the Framingham Offspring Eye Study,<sup>14</sup> showed a strong association of myopia in families. It found that the strength of sibling association was dependent on the age difference (the smaller the age difference, the more similar the siblings were), which suggests a role for shared family environment influencing refractive error.

Family studies can be used to infer the heritability of a disease or trait, which is defined as the proportion of total phenotypic variance ( $V_p$ ) attributed to genetic factors. This can be calculated using the correlation or covariance of the trait between family members and allows the partitioning of the observed population phenotypic variance into additive (A) and dominant (D) genetic components, common or shared (C) and unique (E) environment components, including measurement errors ( $V_A + V_D + V_C + V_E = V_p$ ) using quantitative genetic modeling. A recent large family study calculated a heritability of 55% for SphE<sup>15</sup>; the sib-ship common environment (C) had a major effect on refractive error, explaining approximately 33% of the variance. Twin studies have been described as “the perfect natural experiment to separate familial resemblance from genetic influence.”<sup>16</sup> Recent large twin studies of refractive error have found high heritabilities of 84% to 86%,<sup>17</sup> 89% to 94%,<sup>18</sup> and 75% to 88%.<sup>19</sup> However, unlike family studies, these studies observed no significant effect of common environment.

We therefore set out to perform a large twin study of refractive error to detect shared environmental effects (aspects of the environment that make family members similar), with the particular aim of attempting to estimate the size of the shared common environmental effect based on this study design.

## METHODS

### Subjects

Twin pairs (2208 female, 281 male) aged between 16 and 82 years were recruited through the TwinsUK Adult Twin Registry held at St.

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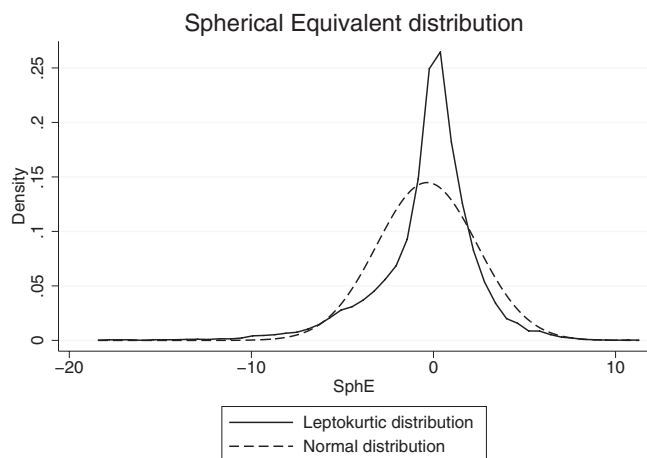
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**FIGURE 1.** Distribution of refractive error (spherical equivalent, in diopters).

Thomas' Hospital in London, where they were invited to undergo eye examination. Details of the registry have been described elsewhere.<sup>20</sup> Full informed consent was obtained, and the research adhered to the tenets of the Declaration of Helsinki. Twins were examined between January 1998 and September 2007. Zygosity was determined by standardized questionnaire,<sup>21</sup> confirmed by DNA short-tandem repeat fingerprinting in cases of uncertainty and genomewide SNP measures. This occurred if the twins or the investigator was in any doubt about true zygosity or when the answers to the standardized questionnaire did not categorize them as definitely monozygotic (MZ) or dizygotic (DZ). Twins were excluded if either or both had undergone procedures, such as cataract surgery (130 subjects), laser or other refractive surgery (42 subjects), or had other ocular surgery or other pathology (2 subjects), that might alter refractive error. Twin pairs were excluded if data from only one of the pair were available (122 subjects) or if zygosity was unknown at the time of analysis (40 twin pairs). The TwinsUK Registry has data on 14,010 twin subjects who have volunteered to participate in research; the 4978 subjects recruited in this study represent 36.2% of those volunteers and include the 1012 subjects previously reported.<sup>17</sup> Reasons for no eye measures included twins who did not attend St. Thomas' Hospital and those who attended before the eye studies were initiated or when no autorefractor was available. These twins were, on average, younger (mean age, 50 years) and were more likely to be male (22% male) than the twins attending, in common with most volunteer cohort studies.

## Measurements

All twin pairs underwent nondilated refraction with an automatic refractor (Humphrey-670; Humphrey Instruments, San Leandro, CA) from 1998 to 2002 and then with an autorefractor (ARM-10; Takagi Seiko, Japan).<sup>17</sup> An automatic refractor measures refractive error by detecting infrared light aligned through the pupil and reflected back by the retina. Refractive error was calculated by the mean spherical equivalent for the both eyes of each subject, measured in diopters, using the standard formula ( $SphE = Sphere + Cylinder/2$ ). If only one eye of a subject was available because of previous surgery or inability to measure the other eye, then this eye's reading was used as the SphE for that subject (28 subjects for the right eye and 21 subjects for the left eye).

## Analytical Approach

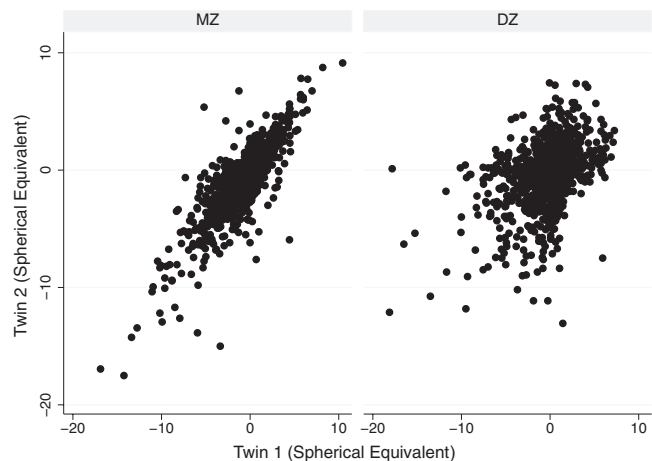
Heritability can be estimated approximately as twice the difference of intraclass correlation coefficients between MZ and DZ twin pairs.<sup>22</sup> The greater the difference between correlations for MZ and DZ twins, the higher the inferred heritability. More accurate heritability modeling using maximum likelihood variance component model fitting was

performed to estimate the phenotypic variance attributable to A, C, D, E, and age, using the application Mx, a structural equation modeling program.<sup>23</sup> We modeled the covariance between MZ and DZ twin pairs to calculate heritability. This model partitions the observed phenotype variance into additive ( $V_A$ ) or dominant ( $V_D$ ) genetic factors (heritability) and common ( $V_C$ ) or unique ( $V_E$ ) environmental factors. The significance of variance components A, C, and D was assessed by dropping each component sequentially from the full model and comparing the submodel fit to the full model. Submodels were compared to full models by hierarchical  $\chi^2$  tests. The difference between log-likelihood values between submodel and full model is asymptotically distributed as  $\chi^2$ , with degrees of freedom (df) equal to the difference in df of submodel and full model. A statistical indicator of goodness-of-fit is the Akaike information criterion (AIC), computed as  $\chi^2 - 2 \text{ df}$ ; submodels are accepted as the best-fitting model if there is no significant loss of fit when a latent variable (A, C, D, or E) is fixed to equal zero. Data handling, preliminary analyses, and all statistical tests were conducted by use of commercial software (STATA/SE10; Stat Corp., College Station, TX).<sup>24</sup> Refractive error was analyzed as a continuous trait using the original diopter scale, but because the trait was leptokurtic (Fig. 1), confirmatory analyses were also performed using normalized rank-transformed data (ranked by SphE and age) to confirm whether model results changed. For the purpose of calculating myopia prevalence, we defined myopia as  $SphE \leq -1$  D, emmetropia as  $-1$  D  $< SphE < 1$  D and hyperopia as  $SphE \geq +1$  D.<sup>10,25</sup>

## RESULTS

Twin pairs (2041 female, 260 male) were included in analysis after exclusion; 1152 were MZ pairs, and 1149 were DZ twin pairs. The mean age of the MZ pairs was 52.6 (SD, 14; range, 16–82) years, and the mean age of the DZ pairs was 54.9 (SD, 11.9; range, 17–80) years. The mean SphE for the twin subjects was  $-0.35$  D and ranged between  $-18.1$  D and  $11$  D; 28% were myopic, 46% were emmetropic, and 26% were hyperopic. Measurements (mean [SD]) were similar for MZ and DZ twins (MZ:  $-0.49$  [2.76]; range,  $-17.5$  to  $+10.44$  D; DZ:  $-0.233$  [2.67]; range,  $-18.12$  to  $+7.44$ ). The frequency distribution of spherical equivalent was leptokurtotic (kurtosis = 7.33) rather than normal, with a left skew (skewedness,  $-1.19$ ; Fig. 1).

The distribution for mean SphE within MZ and DZ twin pairs is plotted in Figure 2, demonstrating a higher correlation within MZ pairs than within DZ pairs. The pairwise intraclass correlation coefficient was 0.85 for MZ twins and 0.45 for DZ twins. The higher correlation of MZ twins suggests a strong



**FIGURE 2.** Scatter plots of spherical equivalent for 1152 DZ and 1149 MZ twin pairs.

**TABLE 1.** Model-Fitting Results for Univariate Analysis of Spherical Equivalent

| Model | $\chi^2$ | $\Delta\chi^2$ | df | <i>P</i> | AIC   |
|-------|----------|----------------|----|----------|-------|
| ACE*  | 23.818   | -              | 3  | <0.001   | 17.8  |
| ADE   | 26.200   | 2.382          | 3  | <0.001   | 20.2  |
| AE    | 26.200   | 2.382          | 4  | <0.001   | 18.2  |
| CE    | 445.542  | 421.721        | 4  | <0.001   | 437.5 |

$\chi^2$ , chi-square goodness-of-fit statistic;  $\Delta\chi^2$ , change in  $\chi^2$  comparing submodel with full model; df, degrees of freedom; *P*, probability that  $\chi^2$  is zero; A, additive genetic effects; C, common environmental effects; D, dominant genetic effects; E, unique environmental effects.  
\* Best-fit model.

genetic contribution for the phenotype variance under the classical twin model. Observations were confirmed by the univariate model-fitting results (Table 1). The best-fit model was the ACE model (with lowest AIC), indicating that additive genetic effects (A), unique environmental effects (E), and shared environmental effects (C) are the most relevant factors to explain individual variation in measures of SphE variance. No significant dominant effects (D) were detected. The heritability estimated for SphE, using this model, was 77% (95% confidence interval [CI], 68%–84%), indicating a strong influence of genetic factors in myopia etiology. Shared and the unique environmental effects explained 7% (95% CI, 0%–15%) and 16% (95% CI, 15%–18%) of the spherical equivalent variance, respectively. Modeling of normalized SphE data yielded similar results: the ACE model was best fitting, with a heritability estimate of 74% (95% CI, 65%–84%), C slightly increased to 9% (95% CI, 0%–18%), and E maintained around 17% (95% CI, 15%–18%).

There was a significant positive correlation between age and SphE ( $r = 0.236$ ;  $P < 0.001$ ). In twins between 20 and 40 years, 43% were myopic; this percentage was reduced to 19% in those older than 70 years (Fig. 3).

The effects of age were also included in the modeling because age effects are likely to be confounded with shared environmental effects, C. When age was included in the model, it explained 5% (95% CI, 3.8%–7.1%) of the population variance; heritability was unaltered, but familial shared effect accounted for only 2% (95% CI, 1.5%–2.8%) of phenotypic variance.

## DISCUSSION

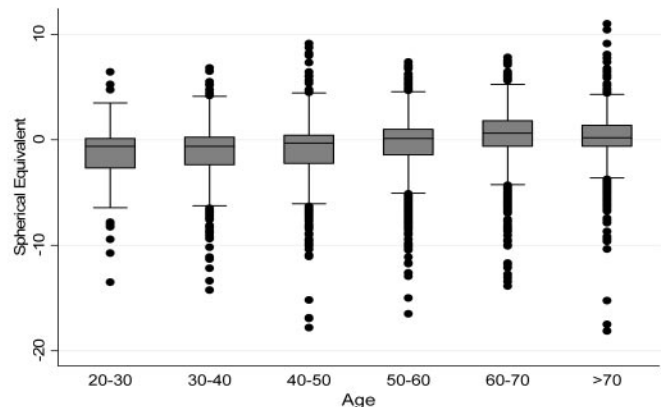
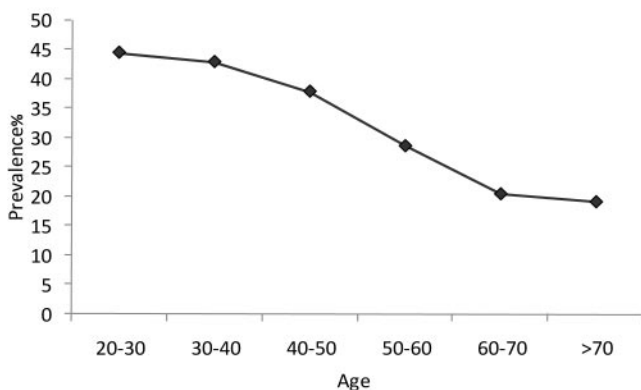
The primary aim of this twin study was to quantify genetic and environmental contributions to refractive error and, in partic-

ular, to examine whether a large twin study supported a significant shared family environmental effect.

The modeling results are consistent with a major role of genetic factors explaining 77% (95% CI, 68%–84%) of the variance in refractive error and a smaller role of shared environment explaining 7% of variation, which was reduced to 2% when age was included in the modeling. Heritability was similar in our previous smaller twin study of 500 pairs that showed genetic effects (A) were responsible for 84% to 86% of variance.<sup>17</sup> A Danish study of 114 twin pairs (heritability 89%–94% for refraction, total refraction, and axial length)<sup>18</sup> and an Australian study of 612 twin pairs (heritability 88%–75% for men and women, respectively) were similar. Both the UK and the Danish studies used parsimonious best-fit AE models, and the Australian study found a sex-limited ADE model was best-fit; none of these twin studies, with relatively large numbers and structural equation genetic modeling techniques, demonstrated any significant shared environmental (C) effect. This study of more than 2000 twin pairs has found only a modest shared environment effect of 2% to 7%.

By contrast, non-twin family studies have found a significant effect of shared environment. The Australian Genes in Myopia (GEM) family study of 132 pedigrees (723 participants, 5–92 years) considered two different common environment definitions: nuclear family shared environment (model 1) and sibship shared environment (model 2). They observed that for both models, common environmental effects ( $c^2$ ) explained approximately 33% of the variance of refractive error, with a heritability of approximately 27% for model 1 and 55% for model 2.<sup>15</sup> One might expect environmental risk factors to be important in myopia, as also demonstrated in the Framingham Offspring Study finding of higher sibling correlations when they were less discordant for age.<sup>14</sup> The prospective Singapore Cohort Study of the Risk Factors for Myopia<sup>26</sup> found a significant correlation between myopia and socioeconomic status (housing type, higher family income, more advanced education of father and mother), even when parental history of myopia and number of books read per week were included in the analysis, supporting a role of shared family environment in myopia etiology.

The tendency of myopia to aggregate within families could be explained by culturally transmitted shared family environment or an inherited genetic susceptibility to the shared environment. The clustering of myopia within a family may be attributed to a culture of shared risk factors such as reading (or protective factors such as outdoor activity) or shared susceptibility genes for myopia in the family. In addition, there may be a gene-environment correlation; potential environmental effects could have a greater effect on families with genetic risk



**FIGURE 3.** Prevalence of myopia in twins UK data by (left) age and (right) box-plot graph of spherical equivalent by age.

than on families with lower genetic susceptibility. The Orinda Longitudinal Study of Myopia (OLSM) attempted to examine these possibilities and found varying results. Although parental myopia was the most powerful predictor of myopia, children with nonmyopic parents did as much near work as those with myopic parents, providing no evidence to support the inherited environment theory.<sup>27</sup> In contrast, more recently the OLSM showed a protective effect of sports and outdoor activities (and no reading effect) and demonstrated that the children of myopic parents participated less than those of nonmyopic parents, supporting a possible role of shared family environment.<sup>28</sup> It may be that both effects are present for different risk factors.

The present twin study of more than 2000 twin pairs is the largest to date and identifies shared environmental effects (C), explaining 7% (95% CI, 0%–15%) of the variance. This shows that shared environment has some influence on twins' similarity for refractive error greater than would be expected by their shared genes. However, this effect is still small and reduces even further when age is included in the model. The question is, why do twin studies consistently observe smaller shared environmental effects than do family studies?

The most obvious reason for this discrepancy between twin and family studies is that twin siblings are better age-matched than non-twin siblings or other family relations<sup>29</sup> and, therefore, are matched for age-related development of myopia. As a function of age, they may also be better matched for other environmental factors associated with myopia, such as sports activity, schooling, and family environment. Within families, age differences have been shown to impact strongly on estimates of heritability. In the GEM study,<sup>15</sup> estimates for common environment remain the same for both models (approximately 33%), but heritability estimates were 27% for a model that defined common environment by nuclear family membership and 55% when defined by sib-pairs membership. The increase in estimated heritability with common environment definition restricted to sib-pairs is likely to be attributed to improved age matching and removal of parental generational age differences. Age differences will give rise to discordance in phenotype definition because the onset of myopia is age related and, to the extent that myopia development is under genetic control, reduces heritability estimates.

Generational and within-family age differences likely play influential roles in detecting shared environmental effects for age-related traits in family studies that include parents and children. For example, in the same GEM study,<sup>15</sup> within-family age differences may account for the detection of large shared environmental effects compared with twin studies, even when shared effects defined to be sib-specific and age-adjusted residuals for spherical equivalence are modeled. This is because age-related environmental covariates covary between family members but not (by definition) between age-matched twins. Although between-family mean age differences are detected by family and twin studies, within-family age differences (and, therefore, age-related environmental covariance) are detected only by family, not twin, study designs. To the extent environmental covariates are related to age and within-family age differences, they will give rise to the detection of shared common environment.

Cohort effects can be defined as disease incidence influenced by birth cohort (i.e., generational) effects and can only be inferred by the use of longitudinal data.<sup>30</sup> Examples of cohort effect in myopia are higher education, urbanization, higher socioeconomic state, and extensive near work, which might have contributed to an increasing myopia prevalence in recent decades.<sup>11,26,31</sup> The prevalence of myopia, in this study, declined from 43% in subjects aged 20 to 40 years to 19% in

subjects aged 70 and older. The decreasing myopia prevalence with age is consistent with other Australian and American adult studies.<sup>8,9</sup> This change may be attributed to a cohort effect (myopia prevalence is increasing in the modern age) or an age course effect (as individuals age, they become less myopic). Mutti and Zadnik<sup>32</sup> suggest that the decreasing prevalence of myopia in adults is caused more by longitudinal changes (age-related tendency to hypermetropia) than to an increasing prevalence of myopia in more recent age cohort effects. In contrast, Rose et al.<sup>33</sup> analyzed raw prevalence data from United States birth cohorts and demonstrated that more recent cohorts had a higher prevalence of myopia than the older cohorts, providing evidence of a birth cohort effect. The Beaver Dam Eye Study also observed that people born in more recent years had higher myopia prevalence than those born earlier.<sup>12</sup> This twin study is a cross-sectional study with a short sampling time frame; it was not possible to assess any possible cohort effect that might have led to better understanding of the processes behind myopia prevalence and its environmental risk factors.

Family studies show higher aggregations of myopia among siblings, which might be attributed to shared environmental factors, than do parent-offspring studies.<sup>34,35</sup> Our classical twin study design assumes MZ and DZ twins on average share the same degree of family environment, which means that environmental effects are independent of zygosity. This is known as the equal environments assumption (EEA).<sup>36</sup> A positive association between educational attainment (school grades, near work activity, intelligence) and myopia has been long demonstrated.<sup>37–39</sup> There is evidence that degree of educational attainment may be more correlated for MZ than for DZ twins,<sup>18,40</sup> but any potential confounding of educational attainment by zygosity is unlikely to violate the twin EEA to a great degree because educational attainment only explains a small fraction of SphE variation (4.4% in the GEM study). The EEA has not been tested for other potential myopia environmental factors such as outdoor activity.

Some additional factors intrinsic to twin study design may further explain the low power to detect family shared effects. When the ACE model is considered and the EEA holds true, the correlation between C and A is often strong and negative and may lead to a confounding between the effects of shared genes and shared environment.<sup>41</sup> Hence, although twin studies (unlike standard family designs) have a strategy for partitioning out familial effects attributable to genetic and common environmental effects, there is still relatively lower power to detect shared environmental compared with polygenic additive effects. The former are often discarded in the name of model parsimony, thereby attributing causal variance to unwarranted genetic factors.<sup>41</sup> These contrast with the power to detect C in the nuclear family shared environment model of the GEM family study.<sup>15</sup> Here different family members were represented with different ages and potential generational effects. Increasing twin sample size and retaining the shared environment in the model should improve the power to detect shared environmental effects, as we have attempted in this study; another approach, without the need to increase total sample, would be to include non-twin siblings in the classical twin design.<sup>42</sup> However, we believe larger numbers than the 2000 twin pairs used in this study would be unlikely to significantly increase the point estimate of shared environmental effects obtained here; they would merely reduce the confidence interval. Hence, extended family designs are likely to be more informative than larger twin samples in detecting environmental effects.

Although we have made comparisons between our twin and the GEM family study that used a novel strategy to partition familial effects into polygenic additive and shared

environmental effects, there is a limitation to these comparisons. The GEM study was based on probands from a refractive laser surgery practice and might have been subject to ascertainment bias. Their complex family study data underwent several transformations, including an ascertainment adjustment based on a population-based dataset (which was based only on subjects older than 43, whereas the mean age in the GEM study was 46). This adds an additional complication to making comparisons because transformed variables on a different scale must be considered as a strictly new phenotype.<sup>41</sup>

Most of the twins in this study are women; although they represent a homogeneous group, without the difficulties of trying to model results with both sexes (with different means and variation),<sup>19,43</sup> the results might not be generalizable to men. By contrast, twins have been shown, on average, to have similar morbidity rates<sup>44</sup> to singletons. We do not believe twin SphE to be significantly different from population-based data: the 37% prevalence of myopia in subjects aged 40 to 50 in this cohort was similar to the prevalence of 35% in the 45-year-olds in the UK 1958 cohort,<sup>45</sup> and a 26.1% prevalence in twins older than 40 is similar to the estimated Western European prevalence of 26.6% calculated by the Eye Diseases Prevalence Research Group.<sup>25</sup> Any ascertainment bias was reduced by the fact that the subjects in this study volunteered to be on our research registry unaware of any specific myopia studies. Phenotyping was performed as part of a larger TwinsUK study, of which autorefractometry was a small part. Axial length measures were not performed for this cohort. This means we are unable to dissect out further the differing effects of axial length, anterior chamber depth, lens thickness, and corneal power.

Our results demonstrate that adult twin studies of sufficient size can detect small shared environmental effects for spherical equivalence. Because of age matching, twin studies are perhaps better placed to detect latent genetic effects for myopia, whereas family studies, by including children and parents with age and potential generational differences, have more power to detect environmental effects that are known to influence the complex age-related trait, myopia.

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