Environmental and Genetic Factors Explain Differences in Intraocular Scattering

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Purpose. To study the relative impact of genetic and environmental factors on the variability of intraocular scattering within a classical twin study.

Methods. A total of 64 twin pairs, 32 monozygotic (MZ) (mean age: 54.9 ± 6.3 years) and 32 dizygotic (DZ) (mean age: 56.4 ± 7.0 years), were measured after a complete ophthalmologic exam had been performed to exclude all ocular pathologies that increase intraocular scatter as cataracts. Intraocular scattering was evaluated by using two different techniques based on a straylight parameter log(S) estimation: a compact optical instrument based in the principle of optical integration and a psychophysical measurement. Intraclass correlation coefficients (ICC) were used as descriptive statistics of twin resemblance, and genetic models were fitted to estimate heritability.

Results. No statistically significant difference was found for MZ and DZ groups for age ($P = 0.203$), best-corrected visual acuity ($P = 0.626$), cataract gradation ($P = 0.701$), sex ($P = 0.941$), optical log(S) ($P = 0.386$), or psychophysical log(S) ($P = 0.568$), with only a minor difference in equivalent sphere ($P = 0.008$). Intraclass correlation coefficients between siblings were similar for scatter parameters: 0.676 in MZ and 0.471 in DZ twins for optical log(S); 0.533 in MZ twins and 0.475 in DZ twins for psychophysical log(S). For equivalent sphere, ICCs were 0.767 in MZ and 0.228 in DZ twins. Conservative estimates of heritability for the measured scattering parameters were 0.39 and 0.20, respectively.

Conclusions. Correlations of intraocular scatter (straylight) parameters in the groups of identical and nonidentical twins were similar. Heritability estimates were of limited magnitude, suggesting that genetic and environmental factors determine the variance of ocular straylight in healthy middle-aged adults.

Keywords: genetics, intraocular scattering, twins

Cataracts are caused by opacities within the clear lens of the eye, degrading the retinal image and vision. Cataracts are a natural aging process that lasts several years in which the optical properties of the crystalline lens gradually degrade the retinal image quality by an increase of ocular aberrations[1] but mainly because of an increase of intraocular scattering that reduces contrast sensitivity.[2,3]

Intraocular scatter and straylight, which are known to naturally increase in subjects starting in their middle age,[4] may degrade the retinal image and vision long before cataracts are diagnosed. Ocular straylight affects visual performance by casting a veiling glare over the retinal image, especially in the presence of bright sources in the visual field. Straylight can be evaluated psychophysically, yielding a value based on its functional impact on vision.[5] Optical measurements of straylight have inherent difficulties due to the large dynamic range required to capture both the peak and the skirts of the eye's point spread function (PSF) that typically spans approximately six orders of magnitude.[6,7] An optical method that overcomes these limitations has been recently developed.[8,9] This technique allows measuring accurately intraocular scatter in subjects with very early stages of cataract development. This is a significant advancement since, although there have been several proposals aiming to quantitatively assess the degree of cataracts, this still remains a challenge.[10–12] Actually, the degree of cataracts is often determined by clinicians by means of the subjective classification based on photographic reference charts, the Lens Opacities Classification System-III (LOCS-III).[13]

Earlier research on the factors affecting the onset of cataracts was usually focused on environmental ones. Antioxidant intake, physical activity, and use of some specific drugs are proposed to be protective agents against cataracts, while age, smoking, being female, alcohol consumption, sun exposure, use of chronic steroids, some types of supplementary nutrition, low educational level, and high body mass index have been characterized as cataract-promoting agents.[14–16] This could mean that to some extent, environmental factors could explain the variance of cataracts. In a previous work by Hammond et al.[17] the variance of nuclear sclerosis scores found among adults could be explained at 48% by means of additive genetic effects, while age accounted for 38% of the variance and the remaining 14% was ascribable to unique environmental exposure. In that study, sclerosis scores were obtained by a subjective determination by using the Oxford Clinical Cataract

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Classification and Grading System and an objective grading system of lens densitometry estimated from Scheimpflug images. For age-related cortical cataracts, genetic models found the influence of a combination of additive and dominant genes, individual environment, and age.[18]

In genetic epidemiology, the observed phenotypes of a trait, such as intraocular scattering, can be partitioned according to biological plausible nature–nurture models into a statistical model representing the contribution of the unobserved genotype and unobserved environmental factors. The variance of the observable phenotypes (σ_ρ^2) can be expressed as a sum of the unobserved underlying variances: $\sigma_\rho^2 = \sigma_G^2 + \sigma_E^2$. Heritability does not explain the mean value of a trait but the proportion of the phenotypic variation in a population that is attributable to genetic variation among individuals: High heritability means that most of the variation that is observed in the population is caused by variation in genotypes; a low heritability means that only a small proportion of observed variability is caused by variation in genotypes. To compare, the classical Mendelian single-gene traits have a heritability of 1, but such clear relations seems to be exceptions. Morphologic traits that usually have large heritability are polygenic; then their heritability will be lower than 1.[19,20] Twin studies (classical twin model) have been described as the perfect natural experiment and are commonly used to estimate heritability in order to analyze the relative weight of genetic and environmental factors on phenotypic variance. Twin studies are based on the comparison of resemblance (concordance or correlation) between identical or monozygotic (MZ) twin pairs and nonidentical or dizygotic (DZ) twin pairs.[21] Monozygotic twins share the same genes, and DZ twins share on average 50% of their segregating genes.[22] Both kind of twins share some environmental factors, such as family, home, and school, while others uniquely affect individual members of a pair, such as accidents and work. The twin design allows comparison of MZ and DZ correlations for estimating heritability by means of the Falconer's formula $[h^2 = 2(r_{MZ} - r_{DZ})]$.[23] A greater similarity between MZ twins compared to DZ twins can therefore be attributed to the additional gene sharing, while a high correlation among DZ twins may indicate an important shared environment effect. Within a classical twin design, the variance of any trait can be accounted for by four possible latent factors: additive genetic effects due to the average effect of the alleles an individual carries (A), nonadditive genetic effects due to dominance on a single gene or to gene-to-gene interactions (D), common or shared environmental influences between both members of a pair (C), and unshared or unique environmental influences on each individual, including measurement error (E). Dividing each of these components by the total variance yields the different standardized components of variance, including heritability.

The main purpose of this study was to determine to what extent the variance of intraocular scattering measurements could be attributable to the different phenotypic components, that is, genetics and environment, in a classical twin study within a group of healthy adult subjects.

Methods

Subjects

The eligible subjects were pairs of adult MZ and DZ twins aged 45 or older without any abnormal ocular condition. Twin pairs were recruited from the Murcia Twin Registry, a population-based twin registry of adult multiples born between 1940 and 1966 in the region of Murcia, Spain.[24] After being informed of the nature of the study and possible consequences, all subjects enrolled provided an informed consent, according to the tenets of the Declaration of Helsinki.

Every prospective subject underwent a complete ophthalmologic exam that included nondilated objective refraction, manifest refraction, uncorrected (UCVA) and best-corrected (BCVA) visual acuity, ocular aberration measurements (Voptica SL, Murcia, Spain), corneal topography (Atlas 9000; Carl Zeiss Meditec AG, Oberkochen, Germany), slit-lamp examination of the anterior segment, indirect ophthalmoscopy and retinal optical coherence tomography (OCT) (Cirrus 5000 OCT; Carl Zeiss Meditec AG). The Voptica instrument is an adaptive optics visual simulator that combines ocular aberration measurement with a Hartmann-Shack wavefront sensor and an aberration correction with a liquid crystal on silicon (LCOS) spatial light modulator.[25]

Exclusion criteria included previous ocular major surgery (cataract, refractive, ocular trauma, and so on) and any corneal or retinal pathology known to increase ocular scattering (epirretinal membrane, corneal scarring, and so on). Concerning cataract diagnosis, two additional exclusion criteria were included: having a nuclear cataract opacification (NO) equal to or higher than grade 3 for the LOCS-III chart and having a BCVA lower than 0.7 (0.155 logMAR). Twin zygosity was ascertained by DNA analysis. When this was not possible, a 12-item questionnaire focusing on the degree of similarity and mistaken identity between twins was used. This questionnaire has been determined by DNA testing to correspond well with zygosity with an agreement in nearly 96% of the cases.[24]

A total of twins were recruited and classified according to zygosity (32 MZ and 32 DZ twin pairs). The MZ and the DZ groups had similar age (range, 47–72 years; mean age MZ = 54.9 ± 6.3 years; mean age DZ = 56.4 ± 7.0 years; $P = 0.204$) and sex distribution (62 female and 66 male; χ^2, $P = 0.289$).

Measurements

The intraocular scattering (straylight) was measured in the two eyes of every subject a few days after the ophthalmologic exam. Two different techniques were used: a psychophysical clinical instrument that obtains the logarithm of the straylight parameter (psychophysical log(S) (C-Quant; Oculus GmBH, Wetzlar, Germany)[4] and a prototype of an optical instrument (optical log(S)).[9] This is based on the optical integration principle. A set of lenses and diaphragms projects an extended source onto the retina and the reflected light is focused into a detector. The illumination and measurement paths are spatially separated to avoid backscattering and spurious reflections. The source has two concentric zones, a disc corresponding to visual angle of 3° (radius) and an annulus (3°–8°). In both zones, light-emitting diodes are square-wave temporally modulated at 483 and 769 Hz for the central and peripheral areas, respectively. A slit-like diaphragm is conjugated to the lower part of the pupil of the measured eye, allowing illumination through the upper part. Light reflected from the central part of the fundus (~1°) is detected through a slit diaphragm conjugated with the upper part of the pupil to avoid overlapping of the illumination and measurement paths. The Fourier transform of the signal reveals the contribution of the annulus and the disc in the reflected signal. The amplitude of the signals from the disc and the annulus, respectively, are used to calculate the optical straylight parameter. In particular, the ratio of the signals from the annulus and the disc is proportional to the ratio of energies in the corresponding angular ranges of the PSF of the eye.[8] A numerical method was applied to calculate the corresponding straylight parameter.[9]

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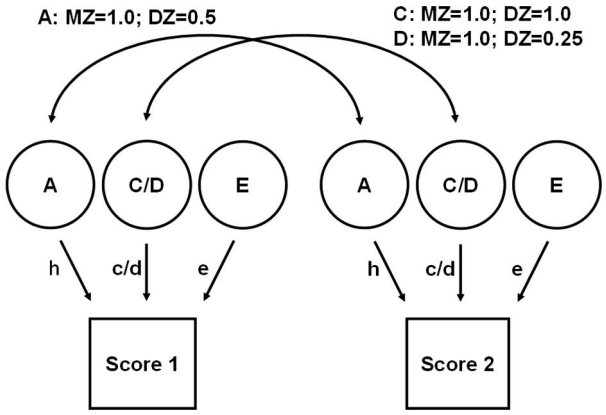

Figure 1. Path model for univariate analysis of a twin study. The observed phenotypes of twins 1 and 2 (scores 1 and 2) are represented in *squares* while latent factors that influence them are represented in *circles* (**A**, **C**, **D**, **E**). Additive (**A**) and dominant (**D**) genetics are correlated by a factor of 1.0 for MZ twins, and by 0.5 (**A**) and 0.25 (**D**), respectively, for DZ twins. Common environment (**C**) is fully correlated for all twins while unshared environment (**E**) is uncorrelated. Regression coefficients of the observed variables on the different latent factors are shown in lowercase: *h* is the regression coefficient of the additive genetic effect. (**C**, **D**) cannot be estimated simultaneously.

Data Analysis

Descriptive analysis was performed using SPSS 19.0 (SPSS, Inc., Chicago, IL, USA), considering a P value below 0.05 as significant. Normal distribution was checked by means of the Kolmogorov-Smirnov test. Pearson correlation was applied to all variables with a normal distribution, while Spearman rank correlation coefficient was calculated in nonnormally distributed variables. Differences between variables were obtained by means of the Student's t-test for normally distributed and the Mann-Whitney U test for nonnormally distributed variables. Manifest refraction was normalized using a rankit procedure prior to genetic analysis.

Intraclass correlation coefficient (ICC) was used instead of Pearson correlation coefficient to avoid problems with twin data dependence when doing the comparison between siblings. In order to estimate the phenotypical influences (A, D, C, or E) on intraocular straylight, the data were analyzed using structural equation modeling (SEM), using the Open Mx package in R.[26] We corrected for mean effects of age and sex, including them as covariates in the analyses, in order to avoid inflating twin estimates of shared environment. One of the limitations of the standard twin design is that it cannot model the effects of both nonadditive genetic (D, dominance) and shared environmental (C, common) influences simultaneously. For this reason, twin studies often test the "ACE" and "ADE" models separately (Fig. 1). C is estimated when DZ correlation is higher than half the MZ correlation, while D is estimated when DZ correlation is less than half that of MZ twins.

To be able to use all data from complete and incomplete pairs, full information maximum likelihood (FIML) estimation with raw data was used. In this method, twice the negative log-likelihood (−2LL) of the data for each family is calculated, and parameters are estimated so that the likelihood of the raw data is maximized. Means, variances, and twin correlations were estimated in a saturated model. Nested models (AE, CE, E) were compared to a full model with likelihood ratio tests (LRT), which are obtained by subtracting −2LL for a restricted nested model from that for a less restricted model ($\chi^2 = (-2LL_0) - (-2LL_1)$. The resulting test statistic has a χ^2 distribution with degrees of freedom (df) equal to the difference in df between the two models. When the fit of a more restrictive (nested) model differs significantly from that of the less restrictive, it implies that the restriction imposed in the nested model does not hold for the available data. The best-fitting model was chosen in each case by deducting the residual deviance of the compared models and by comparing Akaike's information criterion (AIC).

The power of the experimental design to detect heritability based on the current sample size was determined by testing full models (ADE/ACE) versus restricted nested models dropping the genetic components (A+D or A, according to the model) with a 2 or 1 df test, respectively, and α of 5%. The power to detect a broad sense heritability (A+D) of 0.5, 0.6, or 0.8 was 82%, 95%, and 99.9%, respectively, when the contribution of additive and nonadditive effects was equal. The power to detect a narrow sense heritability (A) of 0.4 was 49% when the contribution of additive genetic and shared environmental effects were equal.

Table 1. Pearson Correlation Coefficients for Right Eye (OD) Versus Left Eye (OS) in MZ and DZ Twin Pairs for all the Variables Considered in This Study; All Statistically Significant at $P < 0.001$

OD vs. OS	MZ	DZ
LOCS-III*	0.80	0.90
Manifest refraction*	0.87	0.87
BCVA*	0.48	0.58
Optical log(S)	0.87	0.91
Psychophysical log(S)	0.67	0.56

* Spearman's rank correlation coefficients.

Results

There were no differences in LOCS-III between MZ (range, 1–2.5; mean = 1.41 ± 0.47) and DZ (range, 1–2.5; mean = 1.44 ± 0.47; $P = 0.576$), or in BCVA for MZ (range, 0.7–1.2; mean = 1.13 ± 0.11; –0.05 ± 0.05 logMAR) compared to DZ (range, 0.7–1.2; mean = 1.14 ± 0.11; –0.06 ± 0.05 logMAR; $P = 0.626$). Mean equivalent sphere of the manifest refraction showed a difference of half a diopter (D; $P = 0.008$) between the MZ group (0.01 ± 1.38 D; range, –5.13 to +3.00 D) and the DZ group (+0.54 ± 1.62 D; range, –4.25 to +6.75 D).

When considering all subjects together, the average psychophysical log(S) was slightly higher (1.10 ± 0.19 log(S)) than the average optical log(S) (1.01 ± 0.30 log(S); $P = 0.009$), with the latter showing larger variance. There was no significant difference between MZ and DZ twins for both optical log(S) (–0.05 log(S); $P = 0.386$) and psychophysical log(S) (–0.02 log(S); $P = 0.568$).

The results for right and left eyes were not independent due to high correlation between eyes (Table 1).[27] The average results for both eyes were used to characterize each subject instead of using randomization. A random selection of left or right eye in the group of MZ subjects could be biased if some of the MZ pairs presented a mirror symmetry in some of their morphologic traits.[28]

The comparison between siblings for optical and visual straylight measures and for manifest refraction is presented in Figure 2. Most traits except refractive error in DZ twins show a clear relation between siblings.

Correlations obtained by using the raw data did not take into account the well-known effect of age and sex on lens sclerosis. Table 2 shows the average and range of the ICC stratified by zygosity after adjusting for both age and sex. Monozygotic twin correlations were consistently higher than DZ correlations, suggesting the presence of genetic influence.

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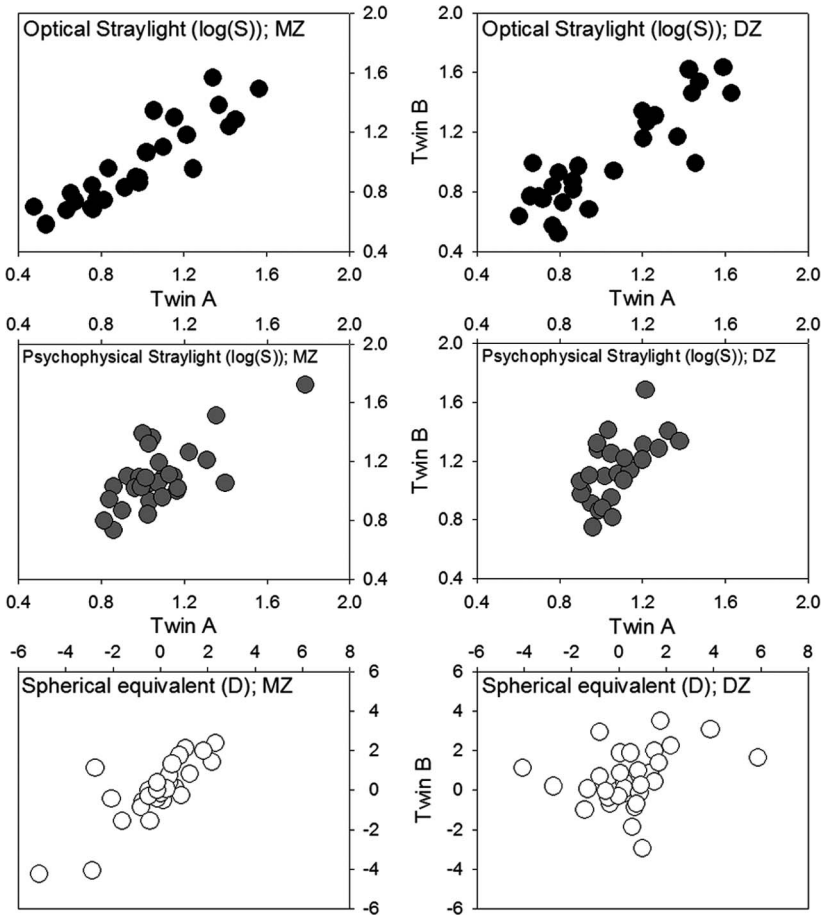

Figure 2. Average results for optical log(S) (*black symbols*) psychophysical log(S) (*gray symbols*) and spherical equivalent (**D**) of the manifest refraction (*white symbols*), for twin A plotted against twin B for monozygotic (*left graphs*) and dizygotic (*right graphs*) twin pairs.

This effect was combined with a DZ correlation more than half that of MZ twins, which also suggests that shared environment was playing a role in the phenotypic trait of intraocular scattering as well. Nevertheless, the 95% confidence intervals around correlations were relatively large, and in many cases overlapped across MZ and DZ twins. This was not the case for manifest refraction, in which the difference in correlation coefficients between MZ and DZ groups was significant.

The pattern of correlations for both intraocular straylight measurements were indicative of a low heritability and relevant effects of shared environmental factors. However, for manifest refraction this pattern suggested the presence of nonadditive genetic influences. Consequently we fitted ACE and ADE genetic models to the first two variables and the last one, respectively (Table 3). For all the three variables compared, the E-only model could be rejected due to both AIC values and statistical significance compared to the full model. The best-fitting models were the AE for optical log(S) and the CE model for psychophysical log(S). However, in both cases, there was not clear indication for selecting one over the other, based on fitting parameters. In fact, the lower bound for additive genetic (A) and shared environment (C) was zero in both variables, meaning that any distinction between the proportions of variance due to the familial factors must be made cautiously. The conservative estimates of heritability obtained in the full models were 39% for optical log(S) and 20% for psychophysical log(S). Estimates for shared environmental effects were in a similar range (27% and 31%, respectively).

Table 2. Intraclass Correlation Coefficients (ICC) and 95% Confidence Intervals (CI95%) for the Logarithm of the Two Straylight Parameters Considered and the Equivalent Sphere of the Manifest Refraction After Correcting for Age and Sex Effects

	MZ	CI95%	DZ	CI95%
Optical log(S)	0.68	0.40 to 0.84	0.47	0.12 to 0.72
Psychophysical log(S)	0.53	0.23 to 0.74	0.48	0.12 to 0.72
Manifest refraction	0.77	0.58 to 0.88	0.23	−0.11 to 0.52

Discussion

The aim of this work was to estimate the values of heritability and environmental factors for intraocular scattering in middle-age adults before cataract. Two different methods to measure intraocular straylight were used in a sample of twin pairs with ages ranging from 47 to 72. One was a prototype based on an optical objective technique that measures the scattering induced by the ocular optical system, and the other was a clinical instrument based on a psychophysical test, which is more related to the functional impact of intraocular scattering. Although both measurements were supposed to provide similar values, due to the intrinsic characteristics of the procedures, there was a significant difference in mean and in variance provided by the two instruments (Fig. 2). The differences found in the genetic models (more oriented to a genetically influenced one for the optical measure, and more environmentally related for the psychophysical one) could

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Table 3. Model-Fitting Results for Analysis of Optical and Psychophysical Intraocular Straylight and Refractive Error

								Parameters of the Fitting Models					
Measure	**Model**	**−2LL**	***df***	**AIC**	**$\Delta\chi^2$**	**Δdf**	***P***	**A**	**95% CI**	**D/C**	**95% CI**	**E**	**95% CI**
Optical log(S)	1. ACE	−109.56	102	−313.56	–	–	–	**0.39**	0.000–0.802	**0.27**	0.000–0.696	**0.34**	0.190–0.589
	2. AE	−108.86	103	−314.86	0.7	1	0.403	**0.68**	0.457–0.812	–	–	**0.32**	0.188–0.543
	3. CE	−108.09	103	−314.09	1.47	1	0.225	–	–	**0.57**	0.361–0.724	**0.43**	0.276–0.639
	4. E	−87.1	104	−295.1	22.46	2	0.000						
Psychophysical log(S)	1. ACE	287.84	110	67.84	–	–	–	**0.20**	0.000–0.699	**0.31**	0.000–0.639	**0.49**	0.293–0.748
	2. AE	288.59	111	66.59	0.75	1	0.386	**0.54**	0.282–0.714	–	–	**0.46**	0.285–0.718
	3. CE	288.12	111	66.12	0.28	1	0.597	–	–	**0.47**	0.242–0.644	**0.53**	0.355–0.758
	4. E	302.32	112	78.32	14.48	2	0.001						
Manifest refraction	1. ADE	330.09	130	70.09	–	–	–	**0.12**	0.000–0.859	**0.67**	0.000–0.872	**0.21**	0.127–0.371
	2. AE	331.39	131	69.39	1.3	1	0.254	**0.78**	0.604–0.873	–	–	**0.22**	0.127–0.396
	3. E	362.64	132	98.64	32.55	2	0.000						

A, D, C, and E, additive genetic, dominant genetic, common environment, and unique environmental effects, respectively; $\Delta\chi^2$, two log-likelihood when comparing each submodel with the full model; *P*, probability that −2LL is zero. On the right side, average results and 95% confidence interval for the A, D/C, and E elements of the univariate fittings obtained are shown. All models adjusted for age and sex.

somehow be related to what the instruments are actually measuring.

The estimate of heritability of intraocular scattering obtained from the genetic models ranged from 20% (for the psychophysical method) to 39% (for the optical method). The contribution of unique environmental factors and random errors (E) to the variance of intraocular scattering was larger in the psychophysical method (49%) than in the optical method (34%). In particular, the E parameter includes those measurements errors that might have affected one subject but not his or her sibling. Therefore, it seems reasonable to interpret that such errors were more likely to occur when a psychophysical process was involved than when a purely objectively assessment of the phenotype (optical) was performed. Interestingly, the estimate of shared environmental effects (C parameter) remained similar in both methods. Approximately 27% of the variance of intraocular scattering measured by the optical method could be explained by commonly shared environmental factors and 31% in the case of the psychophysical method.

It should be mentioned that other nested and most parsimonious models are statistically able to explain our data. The AE and CE models can explain the data of the optical and psychophysical straylight, respectively. Adopting those constrained models would imply a relevant qualitative difference between the measures: a high heritability for the optical measure and only environmental effects for the psychophysical one. However, in both cases, restricted models could be fitted without a significant loss of fit compared to the full ACE model, and there was no robust indication for choosing one or the other. Given the limited size of our sample, which renders a relatively low statistical power, and the high DZ correlations, it seems reasonable to endorse a more conservative full model, without dropping any of the latent influential factors. A larger sample size would increase power and help to discriminate between restricted models, although conclusions based on the heritability estimates would probably not change.

On the other hand, manifest refraction (spherical equivalent) was used here as a reference of a previously known highly genetic influenced trait. In this case, an AE model can be selected instead of the full ADE model, with a heritability estimate of 78%, in good agreement with previous work.[28] Hence, although the statistical power to estimate heritability of intraocular straylight was not large (and the consequence of that was the possibility that different models explained the variance), we were able to determine the influence of a clearly genetic trait as refractive error. That supports the idea that ocular light scatter is a moderately heritable trait, combining genetic effects and the influence of shared and unshared environmental effects.

There is no previous model of heritability of intraocular straylight in healthy adult subjects without a diagnosis of cataracts to compare with. Hammond et al.[17] found that 48% of the variance for nuclear cataracts could be explained by means of genetic factors, with age accounting for 38% of the variance and unique environmental effects for 14%. The assessment of the phenotype was based on a lens sclerosis gradation scale of images taken with a Scheimpflug camera. This method measures backscattered light from the lens and is different from the measurement of straylight reported here (forward scatter). Also the data were recorded in a slightly older cohort that included cases with a diagnosis of cataracts. It is important to note that subjects with any ocular condition known to increase intraocular scattering (including diagnosis of early cataracts) were excluded from this study.

Finally, it might be epidemiologically relevant to identify the sources of the shared environmental effects that partially explain the variance of intraocular scattering. There is a list of promoting and protecting environmental effects for cataracts.[29–32] It might or might not be that those agents act also as intraocular scattering-promoting/protecting factors. One possibility to identify them would be to study past term life habits on our twin sample and try to correlate them with the degree of intraocular scatter. Another possibility would be to study the most discordant MZ twins according to intraocular scatter and check any potential relationship with different life habits. However, given the relatively small sample here, and the high correlations between MZ twins, this approach might be more limited.

In conclusion, we have shown that intraocular scattering is a trait influenced by low to moderate genetic effects and with a relevant contribution of shared environmental effects. The sources in the environment that generate those effects are still unknown, and more epidemiologic work will be required to identify them.

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