Anisometropia Is Independently Associated with Both Spherical and Cylindrical Ametropia

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Purpose. To explore the associations between anisometropia and spherical ametropia, astigmatism, age, and sex.

Method. Associations between the prevalence and magnitude of anisometropia with age, sex, spherical power, and cylindrical power, were assessed in a group of 90,884 subjects attending optometry practices in the United Kingdom. Logistic regression models were used to assess the independent contribution of each explanatory variable.

Results. Logistic regression analyses that included all subjects or just those aged 20 to 40 years showed that spherical ametropia and astigmatism were independently associated with anisometropia (myopes, $P < 1.0E{-}61$; hyperopes, $P < 1.0E{-}11$). Anisometropia was relatively stable between the ages of 20 and 40 years, but then became more common with age, in myopes from the age of 40 years onward ($P < 0.003$) and in hyperopes from the age of 70 years onward ($P < 1.0E{-}6$). Sex was not associated with anisometropia to a clinically significant extent.

Conclusions. This is the first study to show an independent association between anisometropia and both spherical ametropia and astigmatism. The results also suggest that the previously noted increased prevalence of anisometropia with age occurs later in hyperopes than in myopes, once other covariates have been controlled for. However, it could not be ruled out that this latter effect was due to clinical selection bias in our sample. The findings suggest that research projects involving the recruitment of highly ametropic subjects, such as those investigating the genetics of refractive error, may benefit by avoiding the use of stringent inclusion criteria for anisometropia, because otherwise a large proportion of the relevant population will be excluded. (*Invest Ophthalmol Vis Sci.* 2005; 46:4024–4031) DOI:10.1167/iovs.05-0120

Anisometropia, a difference in ocular refraction between fellow eyes, is of great clinical interest because of its intimate association with strabismus and amblyopia. Generally, the correlation in refractive error and ocular component dimensions between right and left eyes is high.[1] This symmetry could arise because ocular component dimensions are under particularly tight genetic control, because both eyes are fine-tuned to the same emmetropic endpoint by visual feedback, or because of a combination of the two mechanisms. In studies using genetic linkage analysis to identify loci conferring susceptibility to refractive errors, anisometropia complicates the assignment of a single phenotypic trait value to subjects. Therefore, unless the linkage analysis framework is flexible enough to permit the analysis of bivariate quantitative traits,[2,3] it is necessary either to ignore anisometropia (for example, by considering only the refractive error in the right eye),[4,5] or to take the average refractive error in the two eyes as the trait value.[6] Because little is known about the etiology of anisometropia, the choice effectively comes down to whether one considers anisometropia to be causally unconnected to ametropia (in which case, it would seem appropriate to ignore it), or whether one considers ametropia to be akin to a "within-subject source of variance" in the genetic determination of refractive error (in which case it would seem appropriate to use the average refraction in the two eyes). A more stringent solution to the problem would be to exclude those subjects who exhibit anisometropia above an arbitrary threshold level, as has sometimes been the practice in myopia control studies. However, this would, again, seem justified only if anisometropia is considered to be etiologically distinct from ametropia per se. Depending on the degree of association between anisometropia and ametropia, this strategy could also lead to the exclusion of a large proportion of potential subjects.

Several studies have documented a positive association between the level of anisometropia and the level of spherical ametropia,[7–13] astigmatism,[7] and age.[14,15] However, only Tong et al.[11] have assessed the extent to which anisometropia and these covariates are independently associated. This is important because of the association that exists between spherical and cylindrical refractive errors[16] and the changes in refraction that occur with age.[15,17] Thus, some of these factors could be implicated due to a guilt-by-association effect, rather than an independent phenomenon that may have etiological relevance.

In the study by Tong et al.,[11] multiple logistic regression was used to identify explanatory variables (risk factors) that were independently associated with the presence of anisometropia in Singaporean schoolchildren aged 7 to 9 years. They found that the presence of myopia (odds ratio [OR] = 4.60), age (OR = 1.19 per year), and sex (OR = 1.19 in females) were all independently associated with anisometropia. The purpose of the present study was to adopt an approach similar to that used by Tong et al., but in a predominantly white population comprising the full age spectrum, to examine the associations between anisometropia and spherical ametropia, astigmatism, age, and sex.

Methods

Subjects

The study population has been described elsewhere.[18,19] Briefly, the spectacle prescriptions of all patients attending 19 optometry practices

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in the north of England between January 2000 and December 2001 were collected. Only the most recent visit was recorded for those who attended more than once during this period. The optometry practices were not selected according to defined epidemiologic sampling criteria; however, apart from a deficit in the number of preteenage subjects, the age-range was highly representative of that of the U.K. population as a whole.[19] Of the 90,884 subjects attending, there were 87,759 with a quantitative spectacle prescription available for both eyes, in which the spherical power was ≥ -40.00 D and $\leq +25.00$ D, the cylindrical power was ≥ -20.00 D and $\leq +20.00$ D, and the patient's age was ≥ 0 years and ≤ 110 years (subjects with data outside these ranges were excluded under the assumption that there had been data entry errors). No correction was made for back vertex distances; however, for the sake of clarity, we refer to spectacle prescription powers as refractive errors or refractive powers. Note that subjects with a balanced prescription (i.e., in whom the refraction in one eye was based on the refraction in the other eye, rather than on the degree of ametropia) were excluded from our analysis. Information relating to ocular history was not available; hence, any subjects who had received refractive or cataract surgery would have been included in our analysis. A breakdown of the subjects' refractive errors by age and sex is given in Supplementary Table S1 (available online at http://www.iovs.org/cgi/content/full/46/11/4024/DC1). Ethics approval for the study was granted by the Cardiff University School of Optometry and Vision Sciences, Human Science Research Ethics Committee. The research adhered to the tenets of the Declaration of Helsinki.

Classification Criteria

We took steps to minimize the potential for spurious associations between anisometropia and ametropia by specifying the refractive error as that in the less ametropic of the two eyes (see the Appendix, available online at http://www.iovs.org/cgi/content/full/46/11/4024/DC1). Subjects were categorized into one of four anisometropia severity groups. For anisometropia defined as the absolute difference in mean spherical equivalent (MSE[20]) powers between the right eye and the left eye (A_{MSE}), the four groups were nonanisometropia, $A_{MSE} <$ 1.00 D; mild anisometropia, $A_{MSE} \geq 1.00$ but < 2.00 D; moderate anisometropia, $A_{MSE} \geq 2.00$ D but < 3.00 D; severe anisometropia, $A_{MSE} \geq 3.00$ D. An analogous system was used to classify anisometropia into four severity groups based on the difference in spherical power between the two eyes (A_{SPH}).

For the preliminary analyses, ametropes were classified into groups with an interval of 1.00 D. Two methods of analysis were performed to examine the relationship between anisometropia and astigmatism. In the first method, refractive errors were transformed using a vectorial approach to give MSE, J_0 and J_{45} powers, as described by Thibos et al.[20] Subjects were grouped according to the MSE power in the less ametropic eye, in 1.00-D intervals. In the second method, the analysis was performed so as to limit the confounding between the magnitudes of spherical and cylindrical powers that occurs with power vector or power matrix methods.[16] Refractive errors for myopic subjects were formatted in minus cylinder notation (thus, spherical power was taken as that in the least minus meridian), whereas prescriptions for hyperopic subjects were formatted in plus cylinder notation (thus, spherical power was taken as that in the least plus meridian). Myopic and hyperopic subjects were (separately) grouped according to the spherical power in the less ametropic eye, in 1.00-D interval categories, as just described.

Subjects were stratified into one of 11 age categories: group 1, age 0 to 9 years; group 2, age 10 to 19 years; group 3, age 20 to 29 years; and so on. Analyses were also performed on only those subjects aged between 20 and 40 years (inclusive).

Statistical Analysis

Because of the non-normal distribution of the data, nonparametric tests were used throughout (SPSS ver.11; SPSS, Chicago, IL). The χ^2 test was used for comparisons of categorical data between groups. The Kruskal-Wallis and Mann-Whitney tests were used for comparisons of continuous measures between groups. The two-sample Kolmogorov-Smirnov test was used to compare distributions. $P < 0.05$ was taken as representing a significant difference. Separate analyses were performed for anisometropia defined as A_{MSE} or A_{SPH}. For the analyses in which the cohort was divided into a large number of subgroups, only subgroups with a sample size of >100 subjects were included.

For the logistic regression analysis, the presence or absence of anisometropia ≥ 1.00 D was used as the dependent variable, whereas age, spherical ametropia, and cylindrical ametropia were considered as continuous independent explanatory variables, along with sex as a binary independent variable. The regression models had to be computed separately in myopic and hyperopic subjects, since preliminary analyses showed that anisometropia tended to increase as ametropia increased on either side of emmetropia (i.e., with increasing hyperopia and with increasing myopia), giving a V-shaped relationship. Also, logistic regression could not be performed using vectorial descriptors of refractive error, for two reasons. First, this would have prevented an assessment of the independent influence of spherical and cylindrical powers, since cylinder and MSE powers are not independent (whereas spherical and cylindrical powers are essentially independent[16]). Second, the change of sign of the J_0 and J_{45} powers depending on cylinder axis again gives rise to V-shaped relationships between these powers and anisometropia (see Fig. 2).

The goodness-of-fit of different logistic regression models was compared by computing the area under the receiver operating characteristic (ROC) curve and the Hosmer-Lemeshow statistic.[21] Each variable in the models was considered individually, to assess their linearity with the logit (specifically, assessing whether the natural logarithm or a quadratic function improved the fit). Models were then chosen by using a backward stepwise approach based on conditional maximum likelihood. Separate models were developed for myopes (spherical power in the least minus meridian in both eyes <0.00 D) and hyperopes (spherical power in the least plus meridian in both eyes >0.00 D). Although these models provided statistically superior fits to the data compared with those of the simpler models, the improvement was modest. Thus, in view of the complexity in interpreting models including nonlinear functions of explanatory variables, only simple models are presented in which age, spherical power, and cylindrical power were each assumed to have a linear relationship with (the logit of) anisometropia.

To examine the association between age and anisometropia in more detail, we computed further logistic regression models in which age was coded as a categorical variable, and odds ratios for anisometropia were calculated for each decade compared with the preceding decade, in subjects aged 20 to 99 years, while other variables were controlled for.

Results

Whether anisometropia was classified as A_{MSE} or A_{SPH} had no effect on the significance of the test results. Therefore, only the results for A_{MSE} are presented, except for the analysis of cylindrical refractive errors where the results of both the vectorial (MSE, J_0 and J_{45}) and nonvectorial (spherical and cylindrical powers) analyses are given.

Anisometropia and Spherical Ametropia

To examine whether the degree of anisometropia and ametropia were positively associated, we compared the prevalence of anisometropia, and its severity, with the MSE power in the subjects' less ametropic eyes. For myopes there was a roughly linear trend of increasing anisometropia prevalence and severity with increasing myopia (Fig. 1A; $\chi^2 = 716$, $df = 27$, $P < 10^{-100}$). In hyperopes, there was a similar trend of increasing prevalence of anisometropia with increasing hyperopia (Fig. 1B; $\chi^2 = 892$, $df = 21$, $P < 10^{-100}$), but the relationship appeared to be less linear.

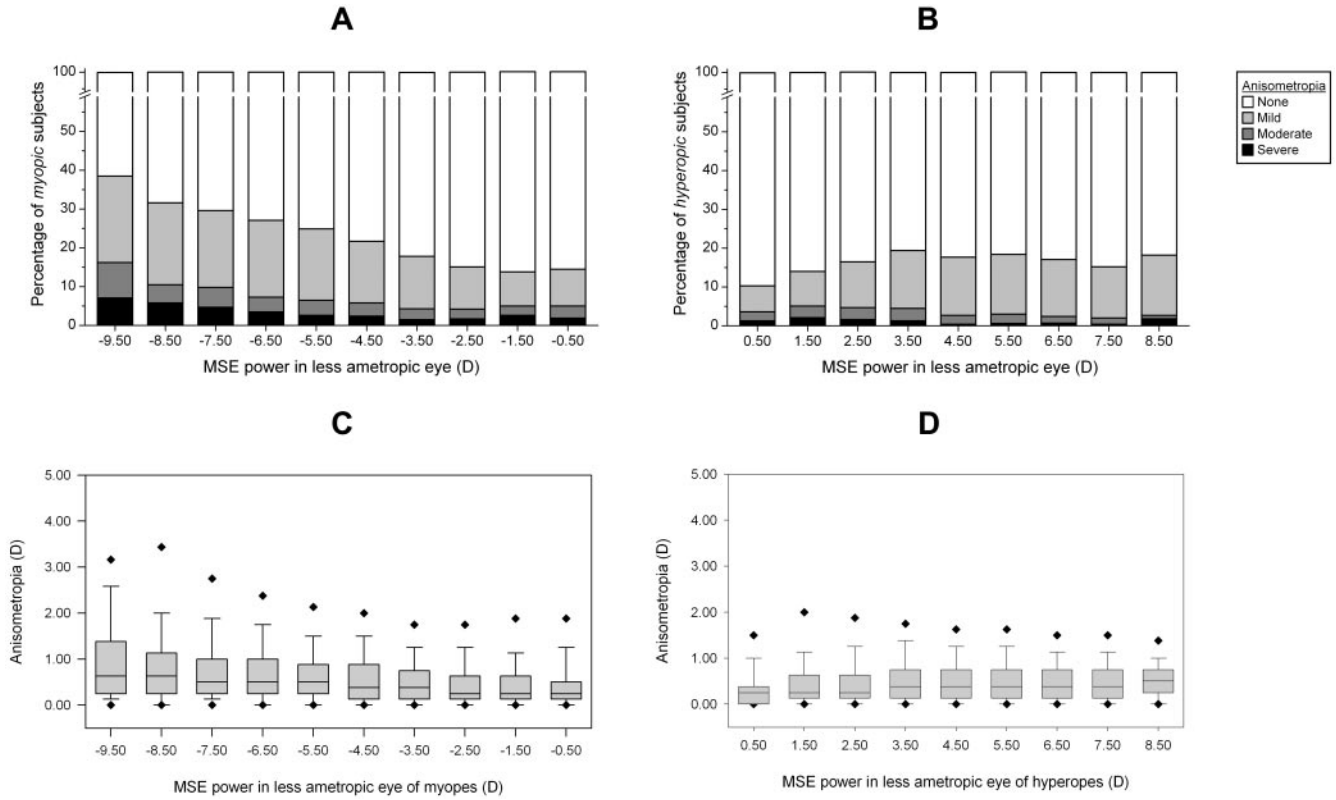

FIGURE 1. Variation in the prevalence and severity of anisometropia with the level of spherical ametropia (MSE). (**A**, **B**) Prevalence of anisometropia in the clinically selected sample, for (**A**) myopes, and (**B**) hyperopes. (**C**, **D**) Level of anisometropia in the same groups of (**C**) myopes and (**D**) hyperopes. *Boxes*: upper and lower quartile ranges; *whiskers*: 90th and 10th percentiles; and *diamonds*: 95th and 5th percentiles. Subjects are grouped in 1.00-D intervals of MSE power in the less ametropic eye, labeled according to the group midpoint. The number of subjects in each group is shown in Supplementary Table S2 (available online at http://www.iovs.org/cgi/content/full/46/11/4024/DC1).

To investigate the relationship between anisometropia and spherical ametropia more quantitatively, we examined the median level of anisometropia in each of the refractive error categories. A positive association was evident in both myopes (Fig. 1C; Kruskal-Wallis test $\chi^2 = 1188$, $df = 9$, $P < 10^{-100}$) and hyperopes (Fig. 1D; Kruskal-Wallis test $\chi^2 = 3263$, $df = 7$, $P < 10^{-100}$). We presume that the relationship between anisometropia and ametropia appears less dramatic when considered in quantitative rather than categorical terms (i.e., in Figs. 1C, 1D, compared with Figs. 1A, 1B) because most subjects in all groups had little or no anisometropia.

Cylindrical Power

In vectorial analyses, both the prevalence and severity of anisometropia varied with the level of astigmatism. Thus, the prevalence of anisometropia in the less ametropic eye of subjects varied with J_0 (Fig. 2A; $\chi^2 = 1630$, $df = 12$, $P < 10^{-100}$) and J_{45} (Fig. 2B; $\chi^2 = 1044$, $df = 12$, $P < 10^{-100}$), as did the level of anisometropia (J_0: Fig. 2E; Kruskal-Wallis test $\chi^2 = 1586$, $df = 4$, $P < 10^{-100}$, J_{45}: Fig. 2F; Kruskal-Wallis test $\chi^2 = 995$, $df = 4$, $P < 10^{-100}$). The relationship between anisometropia and cylindrical power was also evident in nonvectorial analyses. In the less ametropic eyes of myopes, the prevalence of anisometropia increased significantly as cylindrical power increased (Fig. 2C; $\chi^2 = 885$, $df = 12$, $P < 10^{-100}$), as did the level of anisometropia (Fig. 2G; Kruskal-Wallis test $\chi^2 = 893$, $df = 4$, $P < 10^{-100}$). Likewise, in the less ametropic eyes of hyperopes, the prevalence of anisometropia increased significantly as cylindrical power increased (Fig. 2D; $\chi^2 = 275$, $df = 12$, $P < 10^{-52}$), as did the level of anisometropia (Fig. 2H; Kruskal-Wallis test $\chi^2 = 1413$, $df = 4$, $P < 10^{-100}$).

Associations between Anisometropia, Age, and Sex

The prevalence and severity of anisometropia increased significantly with age in this clinically selected group of subjects (Fig. 3A; $\chi^2 = 2377$, $df = 27$, $P < 10^{-100}$) as did its level (Fig. 3C; Kruskal-Wallis test $\chi^2 = 5038$, $df = 9$, $P < 10^{-100}$).

The prevalence of anisometropia was higher in the women than in the men, with the difference just reaching statistical significance (Fig. 3B; $\chi^2 = 9.8$, $df = 3$, $P = 0.02$), and the level of anisometropia was also slightly higher in the women than in the men (Fig. 3D; Mann-Whitney test $z = -3.3$, $P = 0.001$; Kolmogorov-Smirnov test $z = 1.8$, $P = 0.004$). However, in view of the large sample size, and after correcting for multiple-testing, these results suggest that there was no clinically significant difference in the prevalence or level of anisometropia between the sexes.

Logistic Regression Models

Table 1 lists the parameters of the logistic regression models describing the associations between anisometropia and the explanatory variables age, sex, spherical power, and cylindrical power, in hyperopic and in myopic subjects. Separate models were computed for subjects of all ages and for subjects aged between 20 to 40 years, to examine these associations in the whole sample and in subjects in whom childhood refractive development had finished, but before the onset of cataract-induced refractive changes.

In all the models, cylindrical power was the parameter most strongly associated with anisometropia (OR = 1.51–2.16 per diopter). Spherical ametropia also had a highly significant,

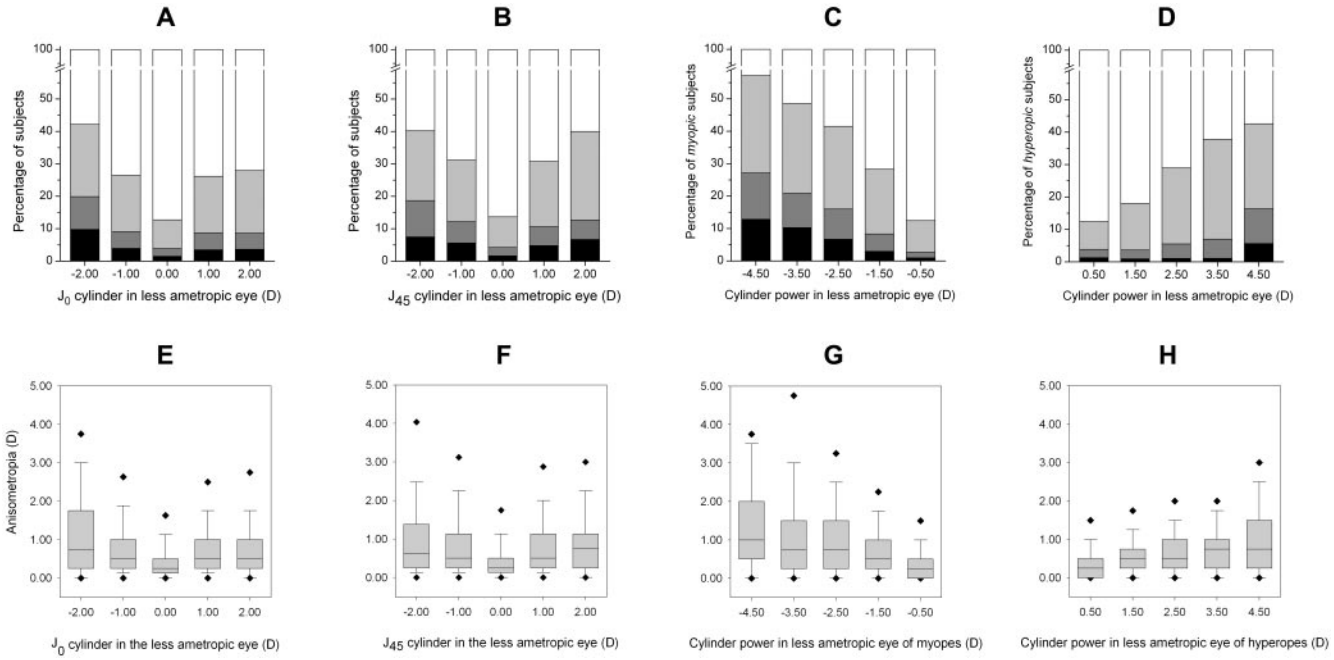

FIGURE 2. Variation in the prevalence and severity of anisometropia with the level of astigmatism. (**A**, **B**, **E**, **F**) Astigmatism represented in vectorial notation; (**C**, **D**, **G**, **H**) astigmatism represented in spherocylinder notation. (**A**, **B**) Prevalence of anisometropia in all subjects, with regard to their level of J_0 and J_{45}, respectively. (**C**, **D**) Prevalence of anisometropia in myopic and hyperopic subjects, respectively. (**A**–**D**) Anisometropia severity level is shown on a gray scale, according to the key in Figure 1. (**E**–**H**) Level of anisometropia in the study groups. *Boxes*: upper and lower quartile ranges; *whiskers*: 90th and 10th percentiles; and *diamonds*: 95th and 5th percentiles. Subjects are grouped in 1.00-D intervals of cylinder, J_0 or J_{45} power in the less ametropic eye, labeled according to the group midpoint. The number of subjects in each group is shown in Supplementary Table S2 (http://www.iovs.org/cgi/content/full/46/11/4024/DC1).

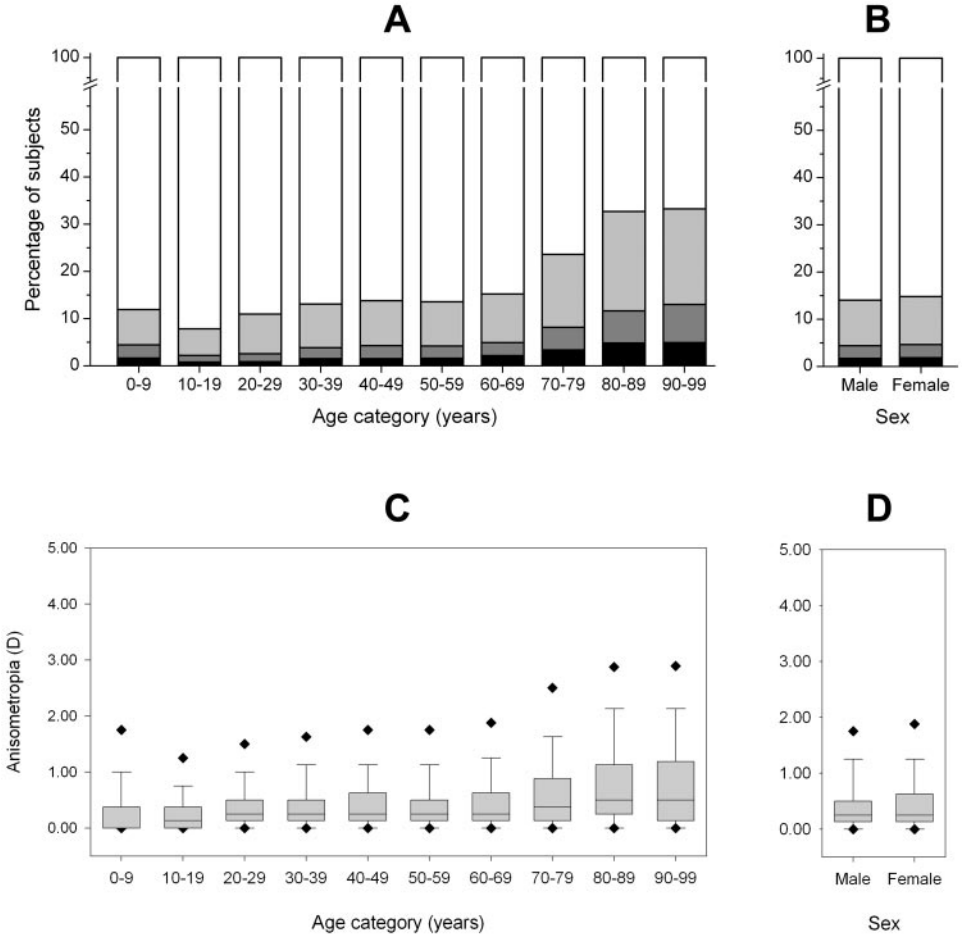

FIGURE 3. Variation in the prevalence and severity of anisometropia with age and sex. (**A**, **D**) Prevalence of anisometropia in the sample, with (**A**) age, and (**B**) sex. Anisometropia severity level is shown on a gray scale, according to the key in Figure 1. (**C**, **D**) Level of anisometropia in the same groups. *Boxes*: upper and lower quartile ranges; *whiskers*: 90th and 10th percentiles; and *diamonds*: 95th and 5th percentiles. The number of subjects in each group is shown in Supplementary Table S2 (http://www.iovs.org/cgi/content/full/46/11/4024/DC1).

TABLE 1. Multiple Logistic Regression Analysis for the Presence of Anisometropia ($A_{SPH} \geq 1.00$ D) with Age Modeled as a Categorical Variable

Model*	Variable†‡	Regression Coefficient	SE of Coefficient	Significance§	Odds Ratio	95% CI of OR	κ‖
Hyperopes	Age (y)	0.00	0.00	NSD	1.00	(1.00–1.00)	¶
All ages (n = 33,716)	Sex (male)	0.05	0.03	NSD	1.06	(0.99–1.13)	¶
ROC = 0.67	Spherical power	0.15	0.01	$P < 0.001$	1.16	(1.14–1.18)	4.75
	Cylindrical power	0.54	0.02	$P < 0.001$	1.71	(1.65–1.78)	1.50
	Constant	−2.54	0.05	$P < 0.001$	0.08	(0.07–0.09)	—
Myopes	Age (y)	0.02	0.00	$P < 0.001$	1.02	(1.02–1.02)	32
All ages (n = 30,681)	Sex (male)	−0.08	0.03	$P < 0.014$	0.92	(0.86–0.98)	¶
ROC = 0.73	Spherical power	−0.16	0.01	$P < 0.001$	0.85	(0.84–0.86)	−4.50
	Cylindrical power	−0.63	0.02	$P < 0.001$	0.53	(0.51–0.55)	−1.25
	Constant	−3.32	0.05	$P < 0.001$	0.04	(0.03–0.04)	—
Hyperopes	Age (y)	0.02	0.01	$P < 0.035$	1.02	(1.00–1.03)	46
Age 20–40 yrs (n = 4,265)	Sex (male)	0.23	0.09	$P < 0.008$	1.26	(1.06–1.50)	¶
ROC = 0.69	Spherical power	0.15	0.02	$P < 0.001$	1.16	(1.11–1.22)	4.75
	Cylindrical power	0.41	0.05	$P < 0.001$	1.51	(1.38–1.65)	1.75
	Constant	−2.80	0.24	$P < 0.001$	0.06	(0.04–0.10)	—
Myopes	Age (y)	0.01	0.00	$P < 0.010$	1.01	(1.00–1.02)	62
Age 20–40 yrs (n = 14,343)	Sex (male)	−0.12	0.05	$P < 0.019$	0.88	(0.80–0.98)	¶
ROC = 0.71	Spherical power	−0.19	0.01	$P < 0.001$	0.83	(0.81–0.85)	−3.75
	Cylindrical power	−0.77	0.03	$P < 0.001$	0.46	(0.43–0.49)	−1.00
	Constant	−3.14	0.14	$P < 0.001$	0.04	(0.03–0.06)	—

Age, spherical power, and cylindrical power were included in each model as continuous explanatory variables, along with sex as a categorical explanatory variable. Hyperopes were classified as subjects with a positive refractive error in the least plus meridian of both eyes. Myopes were classified as subjects with a negative refractive error in the least minus meridian of both eyes.

* Goodness of model fit, given as area under the ROC curve.

† Spherical and cylinder power refer to the less ametropic of the two eyes.

‡ For myopes, both spherical and cylindrical powers are taken to be negative (thus giving increased odds ratios for increasing levels of myopia or astigmatism).

§ NSD, not significantly different.

‖ The value of the variable required to give a twofold increase in the likelihood of subjects' being anisometropic

¶ (Note that not all variables exert sufficient influence to produce a twofold increase in the odds ratio.)

independent association with anisometropia (OR = 1.16–1.21 per diopter). The relationship between anisometropia and ametropia showed remarkable symmetry as refractive errors diverged from zero. Hence, a spherical refractive error of either +4.50 D or −4.50 D led to an approximately twofold increase in the OR for anisometropia, as did a cylindrical power of approximately 1.50 D in hyperopes and myopes.

The association between anisometropia and age appeared to be complex. In myopes, the likelihood of being anisometropic increased with advancing age, when age was examined as a continuous variable (OR = 1.022 per year, 95% CI: 1.020–1.024, for the full age range of subjects, and OR = 1.010 per year, 95% CI: 1.003–1.020, in the 20- to 40-year age group). However, in hyperopes, there was little or no association between age and anisometropia when age was examined as a continuous variable (OR = 1.001 per year, 95% CI: 1.000–1.003 in the full age range, and OR = 1.015, 95% CI: 1.001−1.030, in the 20 to 40 year age group). To explore these associations more closely, additional logistic regression models were computed in which age was analyzed as a categorical variable. In these, odds ratios for anisometropia were calculated for each decade compared with the preceding decade, in subjects aged 20 to 99 years, with adjustment for spherical ametropia, astigmatism, and sex (Table 2).

Of note, this analysis suggests that in myopes, there was a period during their third and fourth decades in which anisometropia was relatively stable (OR per decade not significantly different from 1), followed by a steady increase in the OR with each decade of advancing age from the fifth through to the eighth decades (OR = 1.18–1.55 per decade). Subsequently anisometropia tended to stabilize again when myopes were in their 9th and 10th decades (OR per decade not significantly different from 1). In hyperopes, the pattern was different. After the relatively stable period when the subjects were between the ages of 20 to 39 years, there followed a period during which the probability of a subject's being anisometropic became significantly less likely in the fifth and sixth decades (OR = 0.83–0.84 per decade). After briefly stabilizing again in the seventh decade, hyperopes in their eighth and ninth decades showed an increased likelihood of anisometropia (OR = 1.31–1.43 per decade).

As expected from the analysis of variables in isolation, sex was not closely associated with anisometropia. The strongest effect was in 20- to 40-year-old hyperopes (for men compared with women, OR = 1.26, 95% CI: 1.06–1.50, $P < 0.01$), where the significance level would be borderline when taking into account multiple testing. The large sample size and multiple-testing may also account for the increased likelihood of anisometropia in female compared with male myopes, but in male compared with female hyperopes (thus, for 20- to 40-year-old myopes, in males compared with females, OR = 0.88, 95% CI: 0.80–0.98, $P < 0.02$).

DISCUSSION

Anisometropia and its Association with Spherical Ametropia and Astigmatism

We found an approximately linear increase in the prevalence of anisometropia with increasing myopia. An association between increasing anisometropia and increasing hyperopia was also evident, but the latter relationship appeared to be nonlinear.

TABLE 2. Multiple Logistic Regression Analysis for the Presence of Anisometropia ($A_{SPH} \geq 1.00$ D) with Age Modeled as a Categorical Variable

Model	Variable	Regression Coefficient	SE of Coefficient	Significance	Odds Ratio*	95% CI of OR
Hyperopes	Spherical power	0.13	0.01	$P < 0.001$	1.14	(1.12–1.16)
Age 20–99 y (n = 27,391)	Cylindrical power	0.56	0.02	$P < 0.001$	1.75	(1.67–1.82)
ROC = 0.68	Sex (male)	0.05	0.04	NSD	1.05	(0.98–1.12)
	Age (20s vs. 30s)	0.15	0.09	NSD	1.17	(0.97–1.40)
	(30s vs. 40s)	−0.17	0.08	$P < 0.022$	0.84	(0.73–0.98)
	(40s vs. 50s)	−0.18	0.06	$P < 0.003$	0.83	(0.74–0.94)
	(50s vs. 60s)	−0.01	0.06	NSD	0.99	(0.89–1.11)
	(60s vs. 70s)	0.27	0.06	$P < 0.001$	1.31	(1.17–1.46)
	(70s vs. 80s)	0.36	0.07	$P < 0.001$	1.43	(1.25–1.64)
	(80s vs. 90s)	0.21	0.16	NSD	1.23	(0.89–1.69)
Myopes	Spherical power	−0.16	0.01	$P < 0.001$	0.85	(0.84–0.87)
Age 20–99 y (n = 25,881)	Cylindrical power	−0.63	0.02	$P < 0.001$	0.54	(0.51–0.56)
ROC = 0.72	Sex (male)	−0.06	0.04	NSD	0.94	(0.88–1.01)
	Age (20s vs. 30s)	0.10	0.05	NSD	1.10	(1.00–1.22)
	(30s vs. 40s)	0.23	0.05	$P < 0.001$	1.26	(1.15–1.39)
	(40s vs. 50s)	0.16	0.06	$P < 0.003$	1.18	(1.06–1.31)
	(50s vs. 60s)	0.32	0.07	$P < 0.001$	1.38	(1.20–1.59)
	(60s vs. 70s)	0.44	0.09	$P < 0.001$	1.55	(1.30–1.85)
	(70s vs. 80s)	−0.08	0.12	NSD	0.93	(0.73–1.17)
	(80s vs. 90s)	−0.14	0.25	NSD	0.87	(0.54–1.40)

Spherical and cylinder power were included in each model as continuous explanatory variables, along with age and sex as categorical variables. Hyperopes were classified as subjects with a positive refractive error in the least plus meridian of both eyes. Myopes were classified as subjects with a negative refractive error in the least minus meridian of both eyes. Symboled footnotes are as in Table 1, with the exception of the one shown.

* The odds ratios for age refer to the odds of anisometropia for subjects in one decade compared to subjects in the preceding decade.

The linearity of the relationship between anisometropia and myopia has implications for genetic studies of refractive error, in that the linearity does not suggest a distinct association between anisometropia and spherical ametropia in high myopes compared with low myopes. Instead, the linear trend is consistent with the idea that, etiologically, most cases of high myopia simply represent one tail of the normal refractive distribution. That is to say, cases of high myopia are mostly multifactorial in origin,[22–24] as is believed to be the case in low myopia.[6,25,26] It could be argued that the finding of a linear trend is consistent with the idea that single gene defects are responsible for most cases of high myopia, but this would be the case only if the genetically heterogeneous mutations concerned resulted in rates of (genetically induced) anisometropia that happened to follow on uninterrupted from the trend seen in low myopia.

Previous studies examining the relationship between anisometropia and ametropia have not taken into account a potential source of spurious association between anisometropia and spherical ametropia. As described in the Appendix (http://www.iovs.org/cgi/content/full/46/11/4024/DC1), simulations suggested that the influence of this potential source of bias could be minimized, or even excluded, by specifying the degree of ametropia as that in the less ametropic eye of each subject.

The strength of the association between anisometropia and astigmatism was unexpected. The use of logistic regression to control for the effects of spherical ametropia demonstrated that this association was independent of the relationship between anisometropia and spherical refractive errors. Thus, while an association between anisometropia and astigmatism has been reported previously,[7,12] the results of the present study rule out a guilt-by-association effect. That is, the association between spherical ametropia and astigmatism is not the cause of the association between anisometropia and astigmatism.

The relationship between anisometropia and astigmatism appeared to be qualitatively similar in hyperopes and myopes and in subjects with oblique or nonoblique axes of astigmatism (compare Figs. 2C and 2D). As suggested by Fledelius,[12] this finding implies that astigmatism and anisometropia represent common features of a poorly functioning emmetropization system.

Anisometropia and Its Association with Age and Sex

Weale[14] has tabulated data on the age-related prevalence of anisometropia from a comprehensive review of the literature and noted a linear relationship, with prevalence increasing by ~1.4% for each decade increase in age. Guzowski et al.[7] provided direct confirmation of the increasing prevalence of anisometropia with age in a population of older Australians. Guzowski et al.[7] were able to restrict their analysis to phakic subjects, ruling out the possibility that the effect is the result of intraocular lens implant power mismatches. We found a strong association between anisometropia and age, but our detailed evaluation (Table 2) suggested that the relationship was nonlinear and differed between myopes and hyperopes. However, our results on this issue should be regarded with caution for two reasons. First, we were unable to restrict our analysis to phakic subjects, and second, because of the clinical selection of our study sample. The latter point is relevant, because young, *anisometropic* low hyperopes may tend to visit an optometrist, whereas young, *nonanisometropic* low hyperopes may tend not to. By contrast, of the older low hyperopes, both anisometropes and nonanisometropes may choose to visit an optometrist, to obtain a correction for near vision. This type of selection bias would explain the relative abundance of young, anisometropic hyperopic subjects in the dataset. The overrepresentation of this group would, in turn, mask any trend of increasing anisometropia with increasing age in hyperopic subjects.

The reason for the increase in anisometropia with age is unresolved. Weale[14] has argued that the most obvious candidate—asymmetric nuclear cataract development—may not be the major cause, since the time course of crystalline lens changes is different from that of the increase in anisometropia.

Nevertheless, Guzowski et al.[7] found a higher prevalence of anisometropia in subjects with bilateral (25%) and unilateral (18%) cataract, than in subjects with no cataract (9%). Our results could be interpreted as lending support to this theory too, because development of nuclear cataract would be likely to make subjects myopic, hence explaining why the age-related increase in anisometropia was observed at an earlier age in myopes. Finally, an alternative explanation for the relationship between anisometropia and age would be that nonanisometropes die younger than anisometropes, but this seems highly unlikely.

In accordance with previous studies,[7,11] we found little or no difference in either the prevalence or the severity of anisometropia between the sexes.

The Study Population

How representative was the study population? It is important to note that this study was not a classic epidemiologic investigation. The clinical selection of the subjects meant that persons with refractive errors would have been overrepresented in this dataset, mostly at the expense of emmetropes or low hyperopes. Thus, the prevalence of anisometropia of ~17% in this cohort is approximately double that in the general population of developed countries.[7,12] As well as emmetropes and low hyperopes, a proportion of the subjects who do not visit an optometrist are likely to be unilateral myopes or unilateral hyperopes, and therefore a proportion of this group of anisometropic subjects would not have been sampled.

Perhaps the issue of greatest concern, with respect to the validity of the findings of the present study, relates to our inability to exclude subjects who have anisometropia as a result of unilateral cataract extraction or untreated cataracts. However, we were able to remove the likely influence of this potential source of bias by restricting one set of logistic regression models to subjects of 40 years of age or less (Table 1).

The study population is closely representative of the age distribution of the general population in the United Kingdom, except for a deficit in eye examinations for subjects under 11 years of age.[19] Because this deficit implies that sight tests on children in the United Kingdom are even more heavily biased toward those with refractive errors than is the case for adults, we used a conservative threshold of 20 years of age as a cutoff for two of the sets of regression analyses. This again permitted us to examine the associations between anisometropia and our chosen covariates without the influence of this particular source of bias. A further advantage of the analyses of subjects aged at least 20 years of age is that they are less likely to be influenced by underestimation of the true extent of ametropia. Because our dataset comprised refractive prescriptions, rather than the gold-standard of cycloplegic autorefraction measurements, it is probable that either the full extent of myopia was not measured in some younger subjects, due to incomplete relaxation of accommodation, or that some younger hyperopes were prescribed only a partial correction. Both of these events would be less likely to occur in adults, due to the decline in the amplitude of accommodation with age.

Exclusion of Anisometropic Subjects in Linkage Studies

Approximately 25% of myopes with a refractive error of −6.00 D were anisometropic by more than 1.00 D (Fig. 1) in this U.K. optometric group. However, because the prevalence and severity of anisometropia continues to increase as the level of myopia rises even higher, more and more of the most extremely affected subjects would have to be excluded from high-myopia linkage studies if this amount of anisometropia were chosen as a threshold exclusion level. In the pedigrees that have been unambiguously linked to high-penetrance, autosomal dominant loci for high myopia,[4,5,27,28] approximately 30% of highly myopic subjects ($n = 66$) were anisometropic by >1.00 D. Had all these subjects been excluded, there might have been insufficient power to identify or replicate genetic linkage to many of the loci.

Conclusion

We found that the prevalence and severity of anisometropia in this clinical sample from the United Kingdom increased as the level of ametropia increased. Furthermore, both spherical ametropia and astigmatism were independently associated with anisometropia. With the caveat that we could not rule out an effect of selection bias, we also found that the previously noted increased prevalence of anisometropia with age occurred later in hyperopes than in myopes, once other covariates were controlled for. Sex had little or no effect on anisometropia prevalence or severity. The linearity of the increase in anisometropia with increasing myopia suggests that research projects such as those investigating the genetics of refractive error are justified in avoiding the use of stringent inclusion criteria for anisometropia, because otherwise a large proportion of the relevant population would be excluded.

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