TABLE 1. Prevalence of Age-Related Macular Degeneration in the Japanese Population

	50-59 Years N = 1830	60-69 Years N = 2842	70-74 Years N = 923	Total N = 5595	Overall Standardized Prevalence[a] (95% CI)
Either eye, n (%)					
Early AMD	294 (16.1)	665 (23.4)	288 (31.2)	1247 (22.3)	22.8 (21.7-24.0)
Late AMD	5 (0.27)	15 (0.53)	9 (0.98)	29 (0.52)	0.58 (0.36-0.80)
Soft drusen	561 (30.7)	1173 (41.3)	468 (50.7)	2202 (39.4)	39.2 (37.9-40.5)
Large drusen	216 (11.8)	516 (18.2)	239 (25.9)	971 (17.4)	17.5 (16.5-18.5)
Pigment abnormality	98 (5.4)	222 (7.8)	71 (7.7)	391 (7.0)	7.6 (6.8-8.3)
Bilateral, n (%)					
Early AMD	57 (3.1)	171 (6.0)	101 (10.9)	329 (5.9)	6.1 (5.5-6.8)
Late AMD	0 (0.00)	3 (0.11)	1 (0.11)	4 (0.07)	0.09 (0.00-0.18)
Soft drusen	61 (3.3)	141 (5.0)	67 (7.3)	269 (4.8)	4.6 (4.0-5.1)
Large drusen	45 (2.5)	127 (4.5)	87 (9.4)	259 (4.6)	4.8 (4.2-5.3)
Pigment abnormality	10 (0.5)	32 (1.1)	22 (2.4)	64 (1.1)	1.3 (1.0-1.7)

AMD = age-related macular degeneration; CI = confidence interval.
[a]The prevalence was standardized to the World Health Organization standard population.

TABLE 2. Prevalence of the Phenotype of Age-Related Macular Degeneration in Japanese According to Sex

	Male N = 1977	Female N = 3618	P Value
Early AMD	491 (24.8)	756 (20.9)	.0007
Late AMD	16 (0.81)	13 (0.36)	.025
Soft drusen	765 (38.7)	1437 (39.7)	.454
Large drusen	357 (18.1)	614 (17.0)	.305
Pigment abnormality	192 (9.7)	199 (5.5)	< .0001

AMD = age-related macular degeneration.
Prevalence shown as n (%).

We found similar tendencies regarding age dependence in other features of AMD (soft drusen, large drusen, and pigment abnormalities). Whereas 10.7% of drusen subjects had pigment abnormalities, 60.4% of subjects with pigment abnormalities also had drusen. We found that subjects with larger drusen tended to have pigment abnormalities ($P < .0001$). Reticular pseudodrusen were present in 38 participants (0.68%), including those that were outside of the grid; 17 cases, including a case with late AMD, were within the grid. The prevalence of reticular pseudodrusen was significantly higher among women ($P = .011$), with women accounting for 32 of the 38 subjects (84.2%) with reticular pseudodrusen.

AMD was present in both eyes in 333 of the 1276 participants (20.7%) with any AMD. The overall prevalence of bilateral early AMD was 5.9% (6.1%, standardized), and this value increased from 3.1% in subjects aged 50-59 years to 10.9% in subjects aged ≥70 years. Bilateral late AMD was present in 4 of the 29 participants (13.8%) with any late AMD.

The prevalence of AMD according to sex is shown in Table 2. The prevalence of early and late AMD was significantly higher in men than in women ($P = .0007$ and $P = .025$, respectively). The subtype analysis revealed that the prevalence of RPE abnormalities was significantly higher in men than in women ($P < .0001$). This tendency was found in all age groups ($P = .0001$ in subjects aged 50-59 years and $P = .0002$ in those aged 60-69 years), although this association failed to reach significance in subjects aged ≥70 years ($P = .0694$). The incidences of soft and large drusen were not significantly different according to sex ($P = .454$ and $P = .305$, respectively).

Finally, we evaluated the association between cigarette smoking and the development of AMD (Table 3). The total amount of cigarette smoking was significantly associated with the development of early and late AMD ($P = .0153$ and $P = .0402$, respectively). Particularly, subjects with a Brinkman index greater than 500 had a significantly higher risk for the incidence of early and late AMD ($P = .011$ and $P = .042$, respectively, Supplemental Table 1, available at AJO.com). Never smokers were less likely to have early and late AMD, although these associations did not reach statistical significance ($P = .120$ and $P = .159$, respectively). In the subgroup phenotype analysis, we found strong associations between the presence of RPE abnormalities and both the total amount ($P < .0001$) and status ($P = .0003$) of cigarette smoking. However, these significant associations diminished when we divided the cohort by sex ($P > .05$, Supplemental Table 2, available at AJO.com). We found no significant association between cigarette smoking and the incidence of soft or large drusen ($P > .05$).

DISCUSSION

ALTHOUGH A RECENT META-ANALYSIS IN 4 ASIAN POPULATIONS suggested that the prevalence of early AMD signs

TABLE 3. Association Between Smoking Status and the Phenotype of Age-Related Macular Degeneration in Japanese

	Brinkman Index[a]			Smoking Status, N (%)		
	N	Mean	P Value	Ever (N = 1853)	Never (N = 3742)	P Value
No AMD	4319	169.9 6 344.3		1405 (75.8)	2914 (77.9)	
Early AMD	1247	197.2 6 368.9	.0153	435 (23.5)	812 (21.7)	.120
Late AMD	29	301.9 6 462.2	.0402	13 (0.70)	16 (0.42)	.159
Soft drusen			.939			.069
Absent	3393	177.0 6 348.8		1155 (62.3)	2238 (59.8)	
Present	2202	176.2 6 354.0		698 (37.7)	1504 (40.2)	
Large drusen			.305			.798
Absent	4624	174.5 6 348.7		1528 (82.5)	3096 (82.7)	
Present	971	187.2 6 360.7		325 (17.5)	646 (17.3)	
Pigment abnormality			< .0001			.0003
Absent	5204	171.6 6 346.4		1691 (91.3)	3513 (93.9)	
Present	391	243.9 6 399.9		162 (8.7)	229 (6.1)	

AMD = age-related macular degeneration.
[a]The Brinkman index was calculated by the daily number of cigarettes 3 years.

TABLE 4. Age-Speci☒ Prevalence of Large Drusen (≥125 μm) in Various Populations

Number of Participants Ethnicity Years Study Conducted	Nagahama[a] 6065 Japanese 2008-2010	Los Angeles[23] 6357 Latino 2000-2003	Singapore[7] 3280 Malay 2004-2006	Blue Mountains[28] 3632 White 1992-1994	Beaver Dam[29] 4752 White 1988-1990	Baltimore[27] 1843 Black 1985-1988
Age, y						
50-59 (95% CI)	11.9 (10.2-13.6)	13.6	38.3	1.9	6.8	4.7
60-69 (95% CI)	18.1 (16.6-19.5)	19.3	48.1	5.2	15.8	8.4
70-79 (95% CI)	25.9 (23.1-28.7)[b]	26.3	46.3	11.6	27.8	7.9
Sex						
Male (95% CI)	15.4 (13.6-17.3)	19.7	43.8	4.3	-	-
Female (95% CI)	16.4 (15.2-17.6)	14.9	34.5	5.5	-	-

CI = con☒dence interval.
[a]The prevalence was standardized to the World Health Organization standard population.
[b]The last age group is 70-74 years.

were lower in Asians than in white populations,[12] a wide consensus regarding the prevalence of AMD in Asians has not been established. Several factors make it difficult to compare the prevalences reported in various studies: the differences in photographic and grading techniques, the definition of early AMD, and the age groups used when reporting age-specific rates. Because the prevalence of AMD is strongly related to age and because the age distributions of different populations are not similar, it is important to compare age-specific rates rather than the overall prevalence. However, the details regarding the age-specific rates of the prevalence of AMD have not been reported in the Japanese population because of the small sample sizes of previous studies.[10,11] Thus, the present study should be more reliable than previous studies for comparing the prevalence of AMD in the Japanese population with that in other populations because it includes the age-specific rates of AMD.

Large drusen is an important component of early AMD that has been shown in many longitudinal studies to be predictive of incident late AMD.[3,26] Because the definition of large drusen (≥125 μm) has been defined similarly and measured in all of the populations, we chose to look at large drusen as a manifestation of intermediate AMD in various populations (Table 4). In this comparison, the age-specific prevalence of large drusen in the Japanese was comparable to that reported in white populations and higher than that reported in the black population among persons aged ≥50 years.[27] Of particular interest, our study found high rates of large drusen in all Japanese age groups, which is comparable to the reported prevalence in the Los Angeles Latino eye study (LALES).[23]

TABLE 5. Age-Speci☒ Prevalence of Late Age-Related Macular Degeneration in Various Populations

	Nagahama[a]	Hisayama[10]	Los Angeles[23]	Singapore[7]	Blue Mountains[28]	Beaver Dam[29]	Baltimore[27]	Barbados[30]
N	6065	1486	6357	3280	3632	4752	1843	3444
Ethnicity	Japanese	Japanese	Latino	Malay	White	White	Black	Black
Years	2008-2010	1998	2000-2003	2004-2006	1992-1994	1988-1990	1985-1988	1988-1992
Age, y								
50-59 (95% CI)	0.39 (0.02-0.77)	0.45	0.22	0.21	0.0	0.2	0.35	0.7
60-69 (95% CI)	0.53 (0.26-0.80)	0.88	0.26	0.39	0.5	0.8	0.42	0.4
70-79 (95% CI)	0.99 (0.35-1.63)[b]	0.51	1.50	2.49	2.6	3.7	0.00	1.0
Sex								
Male (95% CI)	0.73 (0.28-1.18)	1.2	0.53	0.46	1.3	1.2	-	0.36
Female (95% CI)	0.30 (0.13-0.48)	0.34	0.38	0.22	2.4	1.9	-	0.89

CI = con☒dence interval.

[a]The prevalence was standardized to the World Health Organization standard population.

[b]The last age group is 70-74 years.

The lesions of late AMD have been defined and graded similarly in most population studies. The age-specific prevalence of late AMD in various populations is shown in Table 5. Although the small number of cases in each study limits these comparisons, the age-specific prevalence of late AMD in Japanese subjects aged < 70 years was comparable with that reported in other populations.[7,10,23,27–30] However, the age-specific prevalence of late AMD in subjects aged 70-79 years was relatively lower than that in the other populations. Caution should be exercised when interpreting our data for the oldest age group because we evaluated subjects aged 70-74 years, which would underestimate the prevalence of AMD in elderly Japanese people. However, considering that a recent meta-analysis in whites reported the predicted late AMD prevalence at 70 and 75 years as 1.4% and 2.8%, respectively, the current study suggests that the prevalence of late AMD is lower in elderly Japanese than in elderly whites.[31] This difference among age groups might be linked to the exceptional change in circumstances in Japan that would lead to potential differences in the lifestyles of these groups; for example, participants aged 66 or younger were born after the end of World War II.

In the present study, the prevalence of early and late AMD was higher in men than in women ($P = .0007$ and $P = .025$, respectively). These results are consistent with those of previous studies in Asian populations, which reported a higher prevalence of AMD among men than among women.[7,11,32,33] Although it is speculated that the reason for this disparity is the higher smoking rate in Asian men compared to women, these sex differences remained in this study even after adjusting for smoking status ($P = .0128$). A similar association was found in LALES.[23] The reason for the higher prevalence of AMD in Japanese men is unclear. A previous genetic study in Japanese subjects[34] may provide insight into this observation because this study suggested that sex had the greatest effect on the development of PCV. In this study, we found sex differences in the prevalence of RPE abnormalities in all age groups. Similar results have been consistently found in Asians[7,10,11] but not in whites.[28,29] Given that RPE atrophy was a prevailing finding in the fellow eyes of patients with PCV,[35] this difference between Asians and whites regarding the background of RPE abnormalities may be associated with the higher prevalence of the particular phenotype of AMD, such as PCV, in Asian populations. In contrast, we did not find a sex difference in the prevalence of drusen. These results are consistent with those of many studies in white populations[6,28,36,37] but are inconsistent with those of previous Japanese studies[11,24] that reported a sex difference in the prevalence of drusen.

Cigarette smoking is a consistently identified risk factor for AMD.[38–40] Although several previous reports confirmed a link between current smoking and AMD in the Japanese,[10,32] this association has not been studied in detail. In this study, we showed that smoking is associated with the development of both early and late AMD in the Japanese, and this is particularly dependent on the total amount of cigarettes smoked. This observed association for smoking is consistent with many previous studies that reported a dose-response effect in whites.[36,39,40] In addition, a strong association between smoking and RPE pigment abnormalities has been revealed. This association is consistent with the Beaver Dam Eye Study, which suggested that smoking is associated with the incidence and progression of RPE pigment abnormalities.[39] However, because this association failed to reach significance when we divided the subjects by sex, it must be evaluated in a larger cohort to conclude whether an association exists between smoking and pigment abnormalities. In contrast to late AMD, the association between cigarette smoking and drusen remains controversial because of the limited number of previous studies. In the present study, we did not find any association between smoking and the incidence of drusen, which is consistent with the result of the LALES.[41]

One of the potential limitations of our study is that it included a low percentage of the overall population, which may have introduced selection bias. It is speculated that women who did not work full time were more likely to participate, resulting in the high female-to-male ratio of this study. Because this study recruited persons who were able to participate on their own, the participants may have been highly health conscious. Further, people working in government and citizen organizations may have been more likely to participate in this study. Finally, people who could not read or move on their own would have experienced difficulty participating in this study, and this bias may have resulted in an underestimated prevalence of late AMD in the Japanese population. However, because the symptoms of early AMD are usually not obvious[2] and would not affect study participation, the magnitude of the selection bias on early AMD prevalence should be negligible. Another limitation was the lack of a detailed evaluation for the subtypes of late AMD (ie, PCV) because of the limited examination in our cohort. A study in which further ophthalmic examinations are performed in the general population is required to identify the prevalence and rate of AMD subtypes in the Japanese population.

Previous reports revealed that early signs of AMD are strong predictors of subsequent advanced stage. The reported 5-year-risk estimates for the development of advanced AMD for each of the scores from 0 to 4 are 0.4%, 3.1%, 11.8%, 25.9%, and 47.3%, respectively.[3] In our study, 1.2% of men aged 70-74 years had a score of 4. If our data are generalizable to all Japanese people, we anticipate that an increased number of Japanese individuals, particularly men, will have late AMD (see Supplemental Figure, available at AJO.com). Applying the reported estimates to our data indicates that a total of 3.1% of men aged 70-74 years may develop advanced AMD in 5 years.

In summary, our study involving > 6000 participants aged ≥50 years provides the first evidence of the age-specific prevalence and detailed characteristics of phenotypes of AMD in the Japanese population. We found that the rates of early AMD in the Japanese population are comparable to those of white populations and that the rates of late AMD were comparable to those of white populations aged < 70 years but were relatively lower in those aged ≥70 years. Further, we found a male-dominant prevalence of RPE pigment abnormalities associated with cigarette smoking. In the Nagahama study, follow-up examination will be carried out 5 years after the baseline survey. Further studies with longitudinal progression of phenotypes of AMD are needed to estimate the relative risk of developing late AMD in the Japanese.

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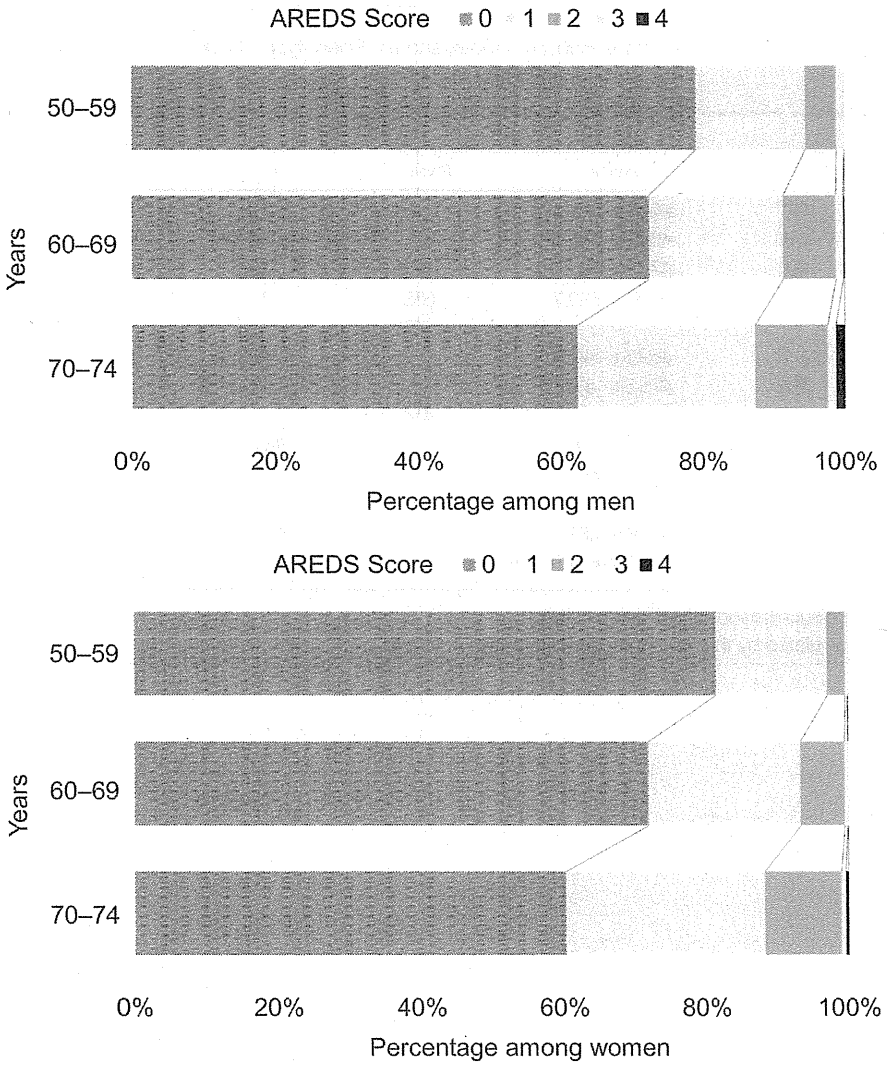

SUPPLEMENTAL FIGURE. Percentages of persons with a risk score for the development of late age-related macular degeneration among men (Top) and women (Bottom) in the Japanese population. Each risk score was calculated by following the severity scale for age-related macular degeneration in the Age-Related Eye Disease Study (AREDS).[3]

SUPPLEMENTAL TABLE 1. Association Between the Brinkman Index and the Risk of Age-Related Macular Degeneration in Japanese

	Brinkman Index[a]			
	Under 500	Over 500	P Value	OR (95% CI)
Early AMD	21.7%	25.5%	.011	1.24 (1.05–1.45)
Late AMD	0.43%	0.97%	.042	2.27 (1.03–5.00)

AMD = age-related macular degeneration; CI = confidence interval; OR = odds ratio.

[a]The Brinkman index was calculated by the daily number of cigarettes 3 years.

SUPPLEMENTAL TABLE 2. Association Between the Brinkman Index and the Phenotype of Age-Related Macular Degeneration in Japanese by Sex

	Male			Female		
	N	Mean BI[a]	P Value	N	Mean BI[a]	P Value
Total	1977	466.0 6 451.3		3618	18.6 6 91.3	
No AMD	1470	461.3 6 449.6		2849	19.6 6 94.9	
Early AMD	491	478.7 6 454.1	.459	756	14.4 6 76.0	.165
Late AMD	16	511.9 6 533.7	.655	13	43.5 6 106.3	.365
Soft drusen			.402			.216
Absent	1212	459.3 6 447.6		2181	20.1 6 95.5	
Present	765	476.8 6 457.1		1437	16.3 6 84.6	
Large drusen			.414			.260
Absent	1620	462.1 6 450.8		3004	19.3 6 94.6	
Present	357	483.7 6 453.7		614	14.8 6 73.1	
Pigment abnormality			.500			.145
Absent	1785	463.8 6 451.3		3419	19.1 6 92.2	
Present	192	486.9 6 451.7		199	9.4 6 74.6	

AMD = age-related macular degeneration; BI = Brinkman index.

[a]The Brinkman index was calculated by the daily number of cigarettes 3 years.

ARTICLE

Nine Loci for Ocular Axial Length Identified through Genome-wide Association Studies, Including Shared Loci with Refractive Error

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Refractive errors are common eye disorders of public health importance worldwide. Ocular axial length (AL) is the major determinant of refraction and thus of myopia and hyperopia. We conducted a meta-analysis of genome-wide association studies for AL, combining 12,531 Europeans and 8,216 Asians. We identified eight genome-wide significant loci for AL (*RSPO1, C3orf26, LAMA2, GJD2, ZNRF3, CD55, MIP,* and *ALPPL2*) and confirmed one previously reported AL locus (*ZC3H11B*). Of the nine loci, five (*LAMA2, GJD2, CD55, ALPPL2,* and *ZC3H11B*) were associated with refraction in 18 independent cohorts (n = 23,591). Differential gene expression was observed for these loci in minus-lens-induced myopia mouse experiments and human ocular tissues. Two of the AL genes, *RSPO1* and *ZNRF3,* are involved in Wnt signaling, a pathway playing a major role in the regulation of eyeball size. This study provides evidence of shared genes between AL and refraction, but importantly also suggests that these traits may have unique pathways.

Introduction

Myopia (nearsightedness), the most common form of refractive errors, is an ocular disorder of major public health importance worldwide, particularly in Asia. About 40% of adults and 80%–90% of children completing high school are myopic in urban areas in East Asian countries, and 10%–20% of them have high myopia.[1,2] Uncorrected myopia and refractive errors are leading causes of visual impairment.[3–6] Furthermore, adults with high myopia are at a substantially higher risk of potentially blinding pathologies, including glaucoma, retinal detachment, and myopic maculopathy.[7] The correction of myopia and refractive errors in general by spectacles, contact lenses, or refractive surgery can entail substantial socioeconomic costs[8,9] and does not treat the underlying mechanism of disease.

Myopia develops primarily from an eye that is excessively elongated axially and thus ocular axial length (AL) is an attractive endophenotype to investigate for several reasons. First, AL alone accounts for more than 40% of variation in refractive errors.[10–12] MRI studies of the orbit have also demonstrated that extremely highly myopic eyes are generally prolate in shape with unusually long ALs, leading to associated visually disabling complications such as posterior staphylomas.[13,14] Second, the heritability of AL (67% to 94%) is consistently higher than that for refraction.[15–18] Furthermore, the measurement of AL (in mm) is more objective, precise, and reproducible compared to assessments of refractive status.

Although more than 30 myopia loci have been implicated in previous linkage and genome-wide association studies (GWASs), there have been few reports of AL-specific loci. A recent GWAS identified an association at *ZC3H11B* for both AL and high myopia in Asians.[19] To identify additional genetic variants that modulate AL, we conducted the largest international GWAS meta-analysis of AL to date in cohorts participating in the Consortium for Refractive Error and Myopia (CREAM).[20,21]

Subjects and Methods

We used a three-stage approach.[20] First, we performed a GWAS meta-analysis in 12,531 European ancestry individuals (stage 1). Second, we tested the cross-ethnic transferability of the associations from this first stage in 8,216 Asian ancestry individuals (stage 2). Lastly, we conducted a meta-analysis combining individuals of European and Asian ancestry, totaling 20,747 individuals (stage 3). We subsequently examined the effect of the associated AL loci on spherical equivalent (SE) in 23,591 individuals from 18 other independent cohorts.

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Table 1. Study Cohorts and Summary of Axial Length Measures

Ethnicity	n	Study	Mean Age (SD), Years	Men, %	Axial Length		
					Mean (SD), mm	Range, mm	Methods of Measurement
European	2,069	ALSPAC Children	15.5 (0.3)	46.5	23.41 (0.87)	20.49–26.57	IOLmaster
	1,316	BATS/TEST	24.6 (11.9)	43.2	23.25 (0.87)	20.03–28.25	IOLmaster
	1,030	BMES	73.8 (7.8)	59.5	23.45 (1.04)	19.94–29.86	IOLmaster
	826	Croatia-Korcula	55.8 (13.4)	35.1	23.19 (1.06)	18.55–28.24	Echoscan US-1800
	352	Croatia-Split	50.0 (14.2)	44.3	23.39 (0.90)	20.98–27.3	Echoscan US-1800
	552	Croatia-Vis	56.0 (14.0)	39.7	23.08 (0.90)	20.09–26.48	Echoscan US-1800
	2,397	ERF4	48.7 (14.2)	55.5	23.22 (1.04)	19.79–27.30	A scan
	503	ORCADES	57.6 (13.7)	43.3	23.70 (1.08)	20.69–28.00	IOLmaster
	1,011	Raine	20.1 (0.4)	51.6	23.56 (0.89)	20.36–27.94	IOLmaster
	676	RS1	78.4 (4.4)	49.0	23.52 (1.06)	20.44–27.72	Lenstar LS900
	1,085	RS2	72.0 (4.7)	47.2	23.50 (1.14)	19.87–28.00	Lenstar LS900
	714	RS3	59.3 (5.8)	42.6	23.56 (1.27)	19.79–28.45	Lenstar LS900 and A scan
Asian	564	BES	62.05 (8.4)	35.5	23.07 (1.15)	19.90–30.36	Lenstar LS900
	1,720	SCES	57.6 (9.0)	51.7	23.95 (1.31)	20.87–32.66	IOLmaster
	926	SCORM	10.8 (0.8)	51.7	24.13 (1.12)	21.05–28.20	Echoscan US-800
	2,141	SiMES	57.6 (10.7)	49.3	23.57 (1.04)	20.48–31.11	IOLmaster
	2,120	SINDI	55.9 (8.8)	51.4	23.41 (1.08)	19.07–31.59	IOLmaster
	745	STARS Parents	38.8 (5.3)	51.0	24.64 (1.51)	21.66–31.57	IOLmaster

Abbreviations are as follows: ALSPAC, Avon Longitudinal Study of Parents and Children; BATS, Brisbane Adolescent Twins Study; TEST, Twins Eye Study in Tasmania; BMES, Blue Mountains Eye Study; ERF, Erasmus Rucphen Family Study; ORCADES, Orkney Complex Disease Study; RS, Rotterdam Study; BES, Beijing Eye Study; SCES, Singapore Chinese Eye Study Singapore; SCORM, Singapore Cohort Study of the Risk Factors for Myopia; SiMES, Singapore Malay Eye Study; SINDI, Singapore Indian Eye Study; STARS, Strabismus, Amblyopia, and Refractive Error Study of Preschool Children; SD, standard deviation.

Study Populations in CREAM

All studies participating in this meta-analysis are part of the CREAM.[20,21] The discovery cohorts included 12,531 European ancestry individuals from 18 studies (Table 1), including ALSPAC Children,[22] BATS/TEST,[23] BMES,[24,25] Croatia-Korcula, Croatia-Split, Croatia-Vis,[26] ERF,[27,28] RS1, RS2, RS3,[29] ORCADES,[30] and RAINE.[31–33] In addition, 8,216 Asian ancestry individuals from six cohorts (Table 1) (BES,[34] SCES,[35] SCORM,[36] SiMES,[37] SINDI,[35] and STARS Parents[38]) were included in the replication stage. General methods, demographics, and phenotyping of the study cohorts have previously been described extensively and are provided in brief in Table 1. All studies were performed with the approval of their local Medical Ethics Committee, and written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Independent Populations in CREAM

To examine whether the loci affecting AL contributed to SE, we studied associations with SE in an additional 18 studies (Table S1 available online): 1958 British Birth Cohort,[39] ALSPAC Mothers,[40] ANZRAG,[41] AREDS 1a1b, AREDS 1c,[15,16] DCCT,[42] EGCUT,[43] FECD,[44] FES,[45] FITSA,[46] GHS 1, GHS 2, KORA,[47–50] OGP Talana,[51] SP2,[52] TwinsUK,[53] WESDR,[54] and Young Finns Study.[55] Only SE (not AL) measures were available in these additional 18 CREAM studies. Detailed study design and methodology of these studies have been published elsewhere. Descriptive data on demographics and phenotypes of these cohorts are shown in brief in Table S1.

Phenotype Measurements

All studies used a similar protocol for ocular phenotype measurements. Eligible participants underwent an ophthalmologic examination including measurements of AL and refraction of both eyes. AL was measured with either optical laser interferometry or A-scan ultrasound biometry (Table 1). Refraction was measured by autorefractor and/or subjective refraction (Table S1). SE was calculated according to the standard formula (SE = sphere+1/2 cylinder).

Genotyping and Imputation

The study samples were genotyped on either the Illumina or Affymetrix platforms. Each study performed SNP imputation with the genotype data, together with the HapMap Phase II ethnically matched reference panels (CEU, JPT+CHB, or the four HapMap populations) on the basis of HapMap build 36 databases (release 22 or 24). The Markov Chain Haplotyping software, IMPUTE[56,57] or MACH,[58] were adopted for imputation. A detailed description regarding genotyping platforms and imputation procedures for each study is provided in Tables S2 and S3.

Stringent quality control of genotype data was applied in each cohort. Samples with low call rates (< 95%) or with gender discrepancies were excluded. Cryptically related samples and outliers in population structure from principal component analyses were