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The Potential of Current Polygenic Risk Scores to Predict High Myopia and Myopic Macular Degeneration in Multiethnic Singapore Adults

Irfahan Kassam, PhD,[1] *Li-Lian Foo, MD,*[2,3] *Carla Lanca, PhD,*[4,5] *LingQian Xu, PhD,*[2] *Quan V. Hoang, MD, PhD,*[2,3,6] *Ching-Yu Cheng, MD, PhD,*[2,6,7] *Pirro Hysi, MD, PhD,*[8,9,10] *Seang-Mei Saw, PhD*[2,3,11]

Purpose: To evaluate the transancestry portability of current myopia polygenic risk scores (PRSs) to predict high myopia (HM) and myopic macular degeneration (MMD) in an Asian population.

Design: Population-based study.

Participants: A total of 5894 adults (2141 Chinese, 1913 Indian, and 1840 Malay) from the Singapore Epidemiology of Eye Diseases study were included in the analysis. The mean ± standard deviation age was 57.05 ± 9.31 years. A total of 361 adults had a diagnosis of HM (spherical equivalent [SE] < −5.00 diopters [D]) from refraction measurements, 240 individuals had a diagnosis of MMD graded by the International Photographic Classification and Grading System for Myopic Maculopathy criteria from fundus photographs, and 3774 individuals were control participants without myopia (SE > −0.5 D).

Methods: The PRS, derived from 687 289 HapMap3 single nucleotide polymorphisms (SNPs) from the largest genome-wide association study of myopia in Europeans to date (n = 260 974), was assessed on its ability to predict patients with HM and MMD versus control participants.

Main Outcome Measures: The primary outcomes were the area under the receiver operating characteristic curve (AUC) to predict HM and MMD.

Results: The PRS had an AUC of 0.73 (95% confidence interval [CI], 0.70−0.75) for HM and 0.66 (95% CI, 0.63−0.70) for MMD versus no myopia. The inclusion of the PRS with other predictors (age, sex, educational attainment [EA], and ancestry; age-by-ancestry, sex-by-ancestry, and EA-by-ancestry interactions; and 20 genotypic principal components) increased the AUC to 0.84 (95% CI, 0.82−0.86) for HM and 0.79 (95% CI, 0.76−0.82) for MMD. Individuals with a PRS in the top 5% showed up to a 4.66 (95% CI, 3.34−6.42) times higher risk of HM developing and up to a 3.43 (95% CI, 2.27−5.05) times higher risk of MMD developing compared with the remaining 95% of individuals.

Conclusions: The PRS is a good predictor for HM and facilitates the identification of high-risk children to prevent myopia progression to HM. In addition, the PRS also predicts MMD and helps to identify high-risk adults with myopia who require closer monitoring for myopia-related complications. *Ophthalmology 2022;129:890-902 © 2022 by the American Academy of Ophthalmology*

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The prevalence of myopia and high myopia (HM) is increasing rapidly,[1] especially among Asians,[2,3] making it a global public health concern.[4] Myopia is associated with sight-threatening diseases in which the risk increases with the degree of myopia. For example, each additional diopter (D) of myopia carries an increased risk of ocular complications developing such as myopic macular degeneration (MMD; 58%), retinal detachment (30%), posterior subcapsular cataract (21%), and open-angle glaucoma (20%).[5] Myopic macular degeneration is a common cause of visual impairment that impacts 2.1% of the world population, with Asians being at particularly higher risk.[6,7]

Myopia is a complex trait arising from an interplay of genetic variation and environmental exposures.[8,9] Increased prevalence of myopia may be attributed partially to changes in lifestyle risk factors, such as the amount of time spent outdoors as well as the amount of near work and education.[8,10−14] Indeed, in countries with a high prevalence of myopia and prevalent environmental risk factors, both the genetic and environmental contributions may play a larger role in the development of HM and myopia-related complications, including MMD.[6] However, within a population in which the environmental exposures are more or less distributed evenly, the individual genetic profile

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may determine the relative disease risk within that population. One of the promises of precision medicine is the ability to predict accurately an individual's risk of common diseases from their DNA sequence.[15–17] Several large-scale genome-wide association studies (GWASs) have identified hundreds of loci associated with myopia,[18–21] with heritability estimates ranging from 5.3% in Asians to 21.4% in Europeans, and a genetic correlation of approximately 0.80 between Asians and Europeans indicating a genetic overlap, but with some differences in effect sizes.[19] The largest GWAS to date was conducted in Europeans and identified 900 trait-associated polymorphisms that explain approximately 18% of the heritability.[20] This figure is expected to rise as more loci are identified with larger sample sizes.

The polygenic architecture of myopia indicates that, although a single variant may not be informative, a liability measure that combines the set of disease-associated variants is necessary to determine individual disease risk. Polygenic risk scores (PRS) summarize the genetic effects from a large number of disease-associated variants and provide a measure of overall risk of individual genetic susceptibility to disease.[22] Several large-scale studies have demonstrated the usefulness of the PRS to stratify myopia risk, although these studies primarily have been performed in individuals of European ancestry.[19,20,23,24] To the best of our knowledge, the highest prediction performance in myopia was achieved by Ghorbani et al[23] in Europeans, in which the PRS explained 10.8% of the refractive error variance, with a moderate improvement in prediction performance when combined with GWAS information from educational years (R^2 = 11.2%). With most large-scale myopia GWASs primarily performed in individuals of European ancestry,[18–21] it remains unclear if these findings are generalizable to diverse adult populations of non-European ancestry. Our previous work in Singapore Chinese children found that the PRS explained 4.1% and 2.2% of teenage spherical equivalent (SE) refractive error and axial length (AL) variance, respectively, and was able to distinguish teenagers with HM from control participants without myopia with an area under the receiver operating characteristic (ROC) curve (AUC) of 0.77.[25]

Few studies have examined the underlying genetics of MMD.[26,27] A candidate gene study by Wong et al[26] tested 50 single nucleotide polymorphisms (SNPs) previously associated with HM for association with patients with HM and MMD (vs control participants with emmetropia or patients with HM without MMD) in Europeans and Asians. Two significantly associated SNPs were identified in the *KCNMA1* gene and downstream from the *GJD2* gene for patients with HM with MMD versus control participants with emmetropia, and none were identified when compared with patients with HM without MMD, indicating limited power because of the sample size, increased complexity in the MMD phenotype, or both. Therefore, because of these power limitations, few, if any, studies have examined the usefulness of a PRS to predict MMD.

In this study, we leveraged summary statistics from the largest GWAS of myopia to date to generate a myopia PRS to predict HM or MMD in an adult Asian population in the Singapore Epidemiology of Eye Diseases (SEED) study, comprising unrelated Chinese (n = 2141), Indian (n = 1913), and Malay (n = 1840) participants. We aimed to evaluate the transancestry portability of the myopia PRS in an Asian population.

Methods

The Singapore Epidemiology of Eye Diseases Dataset

The SEED was a population-based study conducted in Singapore from 2004 through 2011. It comprised Chinese (recruitment conducted in 2009–2011), Indian (recruitment conducted in 2007–2009), and Malay (recruitment conducted in 2004–2006) participants. Full study methodologies have been described previously.[28] A total of 2182 Chinese, 2143 Indian, and 2105 Malay participants had both phenotype and genotype data available for analysis. The study adhered to the tenets of the Declaration of Helsinki, and ethics approval was obtained from the SingHealth Centralised Institute Institutional Review Board. Written informed consent was obtained after the nature of the study was explained.

Inclusion and Exclusion Criteria

Individuals with the following conditions were excluded from the analysis: history of cataract surgery, aphakia or pseudophakia, self-reported refractive surgery in both eyes, or a combination thereof; missing refraction data in both eyes; and combination of cataract surgery in one eye and missing refraction data in the other eye.

Refraction and Biometry Measurements

Individuals underwent a detailed ophthalmologic examination in which noncycloplegic refraction status was determined using an autorefractor (model RK5; Canon). Refraction then was refined subjectively until the best-corrected visual acuity was obtained. The results from subjective refraction were used in the analysis. The SE of refractive error was defined as sphere plus half cylinder. Individuals were classified into myopia groups, with myopia defined as individuals with SE of −0.5 D or less in at least 1 eye. Low myopia, moderate myopia, and HM were defined as $-3.0\ \text{D} < \text{SE} \leq -0.5\ \text{D}$, $-5.0\ \text{D} < \text{SE} \leq -3.0\ \text{D}$, and $\text{SE} \leq -5.0\ \text{D}$ in the worse eye, respectively. Axial length was measured using noncontact partial coherence interferometry (IOL Master version 3.01; Carl Zeiss Meditec).

Grading of Myopic Macular Degeneration

Color fundus photographs centered on the optic disc and fovea were captured for each eye using standardized settings with a nonmydriatic retinal camera (Canon CR-DGi with 10D SLR back; Canon), after inducing cycloplegia. The photographs were graded using the International Photographic Classification and Grading System for Myopic Maculopathy protocol.[29] Based on fundus photograph grading, an eye was considered to have MMD if International Photographic Classification and Grading System for Myopic Maculopathy category 2 (diffuse chorioretinal atrophy), category 3 (patchy chorioretinal atrophy), category 4 (macular atrophy), or any plus lesion were observed.[30] The fundus photographs were graded by 1 of 2 trained graders. Grading of pathologic lesions by 1 retinal specialist and 2 trained graders were compared, and high intergrader agreement (κ coefficient =

0.92) was found. All graders were masked to the participants' characteristics.

Genotype Imputation and Quality Control

Genotype data were assayed on the Illumina 610-Quadv1 and OmniExpress microarrays. For each ancestry, the Michigan Imputation Server was used to impute autosomal SNPs to the 1000 Genomes database (phase 3, version 5) using the EAGLE2+Minimac3 prephasing and imputation pipeline.[31] Preimputation checks included ensuring that all alleles are on the forward strand and coordinates and reference alleles are on the GRCh37 assembly. Preimputation quality control excluded autosomal genotyped SNPs with minor allele frequency of less than 0.05, Hardy-Weinberg equilibrium test P value of less than 10^{-6}, SNP missingness call rate of more than 5%, and genotyped SNPs that are not in the 1000 Genomes (phase 3) reference panel using PLINK.[32] Approximately 78 million autosomal SNPs were available after imputation in each ancestry. Quality control after imputation within each ancestry excluded imputed SNPs with minor allele frequency of less than 0.05, Hardy-Weinberg equilibrium test P values of less than 10^{-6}, imputation quality scores of less than 0.90 and multiallelic SNPs. Approximately 4 million imputed autosomal SNPs were included in the final dataset for each ancestry. A total of 3 466 499 SNPs were in common between SEED and data from Hysi et al,[20] of which 796 522 are HapMap3 SNPs.[33] Autosomal genetic relationship matrices between individuals were calculated from the full set of imputed SNPs in each ancestry separately using the *−make-grm* command in the Genome-wide Complex Trait Analysis (GCTA) 1.93 software package.[34] Unrelated individuals were identified with off-diagonal elements of the genetic relationship matrix of less than 0.10 (i.e., equivalent to excluding approximately third-degree relatives or closer) using the *−grm-cutoff* command in GCTA within each ancestry. A total of 5894 unrelated individuals (2141 Chinese, 1913 Indian, and 1840 Malay) in SEED remained and were included in downstream analyses.

Identifying Ancestral Outliers

Genetic ancestry for each individual in SEED was confirmed by multidimensional scaling analysis (Fig S1, available at www.aaojournal.org). Genotype data from SEED was combined with data from the 1000 Genomes (phase 3) dataset comprising 2504 individuals from 26 populations. Multidimensional scaling analysis was performed on the combined set of individuals and 424 518 HapMap3 SNPs[33] that were filtered on minor allele frequency of less than 0.05, Hardy-Weinberg equilibrium test P value of less than 10^{-6}, and genotype call rate of less than 0.01 using PLINK.[32] Ancestral outliers were defined as individuals more than 3 times the interquartile range from the median of the first 2 multidimensional scaling components. A total of 235 individuals (12 Chinese, 177 Indian, and 46 Malay) were identified as ancestral outliers.

Generating Polygenic Risk Scores

Summary statistics from the largest GWAS of myopia to date (n = 542 934) from Hysi et al[20] (see "URLs" below) was used to generate a myopia PRS in SEED. Importantly, the publicly available summary statistics do not include data from the 23andMe customer base, and therefore represent a subset of 260 974 individuals from the study. The PRS for each individual, j, is defined as the weighted sum of SNP allele counts and can be written as:

$$\mathrm{PRS}_j = \sum_{i=1}^{M} \hat{b}_i x_{ij}, \quad (1)$$

where M is the number of SNPs included in the PRS; $\hat{b}_i$ is the per-allele weight (e.g., effect size estimate from the GWAS) for SNP i, and x_{ij} is the number reference alleles for SNP i and individual j. Because effect sizes were not available in the summary data, we estimated $\hat{b}_i$ and the corresponding standard error from the z-statistic, allele frequency, and sample size using equation 6 from Zhu et al.[35]

The myopia PRS was generated in each of the 3 ancestries in SEED using the SBayesS method implemented in the Genome-wide Complex Trait Bayesian (GCTB) software,[36] which performed best among 6 other approaches in our benchmarking analysis (Supplemental material, available at www.aaojournal.org). SBayesS takes as input GWAS summary statistics and a linkage disequilibrium (LD) reference panel to estimate the joint effects of all SNPs using the LD information from the reference panel. Shrunk sparse LD matrices generated by Lloyd-Jones et al[37] (see "URLs" below) were used, which were built using 1.09 million HapMap3 SNPs from a subset of 50 000 unrelated Europeans from the UK Biobank.[38] SBayesS was run with the default parameters, with variants in the MHC region excluded because of the complexity of this region using the *−exclude-mhc* command. The Markov chain Monte Carlo (MCMC) was performed with 50 000 iterations (*−chain-length 50 000* command), 20 000 burn in (*−burn-in 20 000* command), and frequency of 10 (*−out-freq 10* command). The number of chains was set to 4 (*−num-chains 4* command). The PRS was calculated for each individual in SEED by multiplying the best guess genotypes for 687 289 HapMap3 SNPs in common with the SEED data, the Hysi et al data,[20] and the LD reference panel by the effect sizes reweighted by SBayesS using the PLINK score function.[32] The PRS scores then were standardized to have a mean of 0 and a variance of 1. The sign of the PRS was reversed so that the higher score was associated with higher risk of myopia.

Association between Polygenic Risk Scores and Myopia Phenotypes

The nonparametric Kruskal-Wallis test was used to test for differences in PRS across the 3 ancestries and myopia groups. The association between SE and AL (in the worse eye) and the PRS was tested in SEED using multivariate linear regression. All continuous phenotypes were standardized to have a mean of 0 and a variance of 1. The model can be written as:

$$y = \mu + \sum_{i=1}^{T} \beta_i x_i + \beta_{PRS} PRS + e, \quad (2)$$

where y is an $n \times 1$ vector of SE or AL values, with sample size n; μ is the intercept; β_i is the fixed effect estimate for the ith basic covariate, x_i; β_{PRS} is the fixed effect estimate for the *PRS*; and e is the residual. The T basic covariates included age, sex, ancestry, age-by-ancestry and sex-by-ancestry interactions, and 20 genotypic principal components (PCs) derived from the genetic relationship matrices using the *−pca* command in GCTA.[34] Height and height-by-ancestry interaction additionally were included as basic covariates for AL. Significance of the PRS was assessed with a 1-degree of freedom analysis of variance (ANOVA) by comparing a model with only basic covariates (basic model) versus a basic model that included the PRS. The effect size (in standard deviation [SD] units), standard error, 95% confidence interval (CI), association P value, and incremental R^2 value were used to assess the strength of associations. Incremental R^2 (hereafter referred to as R^2) was defined as the gain in the adjusted R^2 value when the PRS is added

as a covariate to the regression of the phenotype on the set of basic covariates and is interpreted as the proportion of phenotypic variance explained by the PRS. The equality of PRS effect sizes for SE and AL across ancestries was tested by including a PRS-by-ancestry interaction term to equation 2. Significance of the PRS-by-ancestry interaction term was assessed with a 2-degrees of freedom ANOVA by comparing the interaction model with the model in equation 2. The robustness of the results was tested by including educational attainment (EA) and an EA-by-ancestry interaction in the set of basic covariates to capture nongenetic effects. Educational attainment was treated as a categorical variable with 5 levels: no formal education (n = 1107); primary education (n = 2201); O or N levels (n = 1491); A levels, polytechnic, diploma, or certificate (n = 637); university education (n = 451); and others (n = 5). Significance of the PRS was assessed in the same way as described above.

Prediction Performance of the Polygenic Risk Score on High Myopia and Myopic Macular Degeneration

The ROC curve and the corresponding AUC were used to assess the ability of the PRS to distinguish between individuals with HM versus those with no HM and control participants without myopia and between individuals with MMD versus those with no MMD and control participants without myopia. The AUC relates the false-positive rate (specificity) with the true-positive rate (sensitivity) and takes on values between 0.5 and 1, which represent a PRS with no and perfect discriminatory power, respectively. Logistic regression was performed on a binary variable (i.e., patient with HM or MMD vs. control participant) as the dependent variable and considered age, sex, ancestry, EA, 20 genotypic PCs, and the PRS as the independent variables using the *glm* function with a binomial link in R software version 3.6.0 (R Foundation for Statistical Computing). A total of 3 models were tested. Model 1 included only the basic covariates (age, sex, ancestry, and EA; age-by-ancestry, sex-by-ancestry, and EA-by-ancestry interactions; and 20 genotypic PCs) as the independent variables; model 2 was a univariate model with only the PRS as the independent variable; and model 3 included the basic covariates and the PRS (i.e., basic covariates + PRS) as the independent variables. The *roc* command implemented in the *pROC* library in R software version 3.6.0 then was used to assess the ROC and AUC. DeLong's test implemented in the *roc.test* command from the *pROC* library in R software version 3.6.0 was used to compare the AUC between ROC curves from the nested models. In particular, model 3 (basic covariates + PRS) was compared against model 1 (basic covariates) to assess the significance of adding the PRS to the basic model. To determine if the AUC estimates were robust to imbalance between the patients with myopia and control groups, we downsampled control groups by randomly selecting individuals in the control group to match the number of samples in the cases group and estimated the AUC. This was performed 1000 times. Finally, odds ratios were calculated for individuals in the top fifth, tenth, twenty-fifth, and fiftieth percentiles of the PRS distribution versus the remaining individuals. *P* values were calculated with a chi-square test from the 2 × 2 table of myopia status versus PRS risk group using the *oddsratio* command implemented in the *epitools* library in R software version 3.6.0.

URLs

Below is a list of software and publically available datasets that were used in this study.

1. GCTB: https://cnsgenomics.com/software/gctb/#Overview
2. GCTA: https://cnsgenomics.com/software/gcta/#Overview
3. LDpred: https://github.com/bvilhjal/ldpred
4. PLINK: https://www.cog-genomics.org/plink/1.9/
5. Shrunk sparse LD matrices generated by Lloyd-Jones et al[37]: https://cnsgenomics.com/software/gctb/#Download
6. GWAS summary statistics from Hysi et al[20]: ftp://twinr-ftp.kcl.ac.uk/Refractive_Error_MetaAnalysis_2020
7. GWAS summary statistics from Jiang et al[39]: https://yanglab.westlake.edu.cn/resources/fastgwa_data/UKB/50.v1.1.fastGWA.gz

Results

Study Participants

A total of 5894 unrelated adults (2141 Chinese, 1913 Indian, and 1840 Malay) in SEED with both phenotype and genotype data were available for analysis after quality control. The mean ± SD age among SEED participants was 57.05 ± 9.31 years and was significantly different across the 3 ancestries ($P = 4.55 \times 10^{-11}$), ranging from 55.83 ± 8.76 years in Indian participants to 57.86 ± 10.40 years in Malay participants. The proportion of female participants was 49.10% ($P = 0.32$). The mean ± SD SE was −0.53 ± 2.48 D, differing from −1.07 ± 2.87 D in Chinese participants to −0.21 ± 2.27 D in Indian participants ($P = 8.87 \times 10^{-29}$). Similarly, the mean ± SD AL was 23.72 ± 1.25 mm, varying from 23.45 ± 1.11 mm in Indian participants to 24.05 ± 1.41 mm in Chinese participants ($P = 1.73 \times 10^{-51}$). The proportion of individuals with no myopia was highest in Malay participants (70.71%), and the proportion of individuals with low myopia (26.72%), moderate myopia (9.57%), and HM (9.81%) was highest in Chinese participants. An MMD diagnosis was highest among Malay participants (5.43%) compared with Chinese participants (4.67%) and Indian participants (2.09%; $P = 3.16 \times 10^{-7}$). Full details are in Table 1.

Polygenic Risk Score

Figure 1 shows that the distribution of the myopia PRS is significantly different across the 3 ancestries ($P = 9.27 \times 10^{-149}$), with Chinese participants, on average, showing a higher PRS as compared with Indian and Malay participants. The PRS increased with the degree of myopia, where higher myopia severity corresponded to a higher PRS ($P = 3.44 \times 10^{-71}$). Individuals with MMD showed a higher PRS, on average, as compared with those without MMD ($P = 2.36 \times 10^{-10}$).

Accuracy of the Polygenic Risk Score for Prediction of Spherical Equivalent and Axial Length

A basic model including age, sex, ancestry, age-by-ancestry and sex-by-ancestry interactions, and 20 genotypic PCs as covariates (height and height-by-ancestry interaction additionally were included as covariates for AL) explained 7.71% and 12.87% of the SE and AL variance, respectively. Adding the PRS to the basic model showed that a higher PRS was associated with a more myopic SE (Fig 2), with 5.09% (95% CI, 4.00%–6.18%; $P = 1.62 \times 10^{-74}$, ANOVA) of SE variance explained by the PRS (Fig 3). Similarly, higher PRS was associated with longer AL, with 3.31% (95% CI, 2.42%–4.21%; $P = 1.38 \times 10^{-51}$, ANOVA) of AL variance explained by the PRS. A significant interaction was observed between the PRS and ancestry for both SE ($P = 3.25 \times 10^{-7}$, ANOVA) and AL ($P = 3.59 \times 10^{-6}$, ANOVA), indicating variation in PRS effect sizes across the 3 ancestries. To investigate this further, we performed a stratified analysis in each ancestry

Table 1. Summary Statistics for the Singapore Epidemiology of Eye Diseases Cohort

	Singapore Epidemiology of Eye Diseases Cohort	Chinese Participants	Indian Participants	Malay Participants	P Value (Global)*	P Value, Pairwise Comparisons†		
						Chinese vs. Indian Participants	*Chinese vs. Malay Participants*	*Indian vs. Malay Participants*
Sample size	5894	2141	1913	1840	—	—	—	—
Age (yrs), mean ± SD	57.05 ± 9.31	57.43 ± 8.66	55.83 ± 8.76	57.86 ± 10.40)	4.55×10^{-11}	2.17×10^{-9}	1	2.38×10^{-8}
Female participants, no. (%)	2894 (49.10)	1048 (48.95)	918 (47.99)	928 (50.43)	0.32	—	—	—
SE in the worse eye (D), mean ± SD	−0.53 ± 2.48	−1.07 ± 2.87	−0.21 ± 2.27	−0.25 ± 2.06	8.87×10^{-29}	2.64×10^{-24}	9.63×10^{-19}	0.16
Axial length in the worse eye (mm), mean ± SD	23.72 ± 1.25	24.05 ± 1.41	23.45 ± 1.11	23.62 ± 1.10	1.73×10^{-51}	2.18×10^{-48}	3.35×10^{-22}	3.63×10^{-8}
Myopia status, no. (%)								
MMD	240 (4.07)	100 (4.67)	40 (2.09)	100 (5.43)	3.16×10^{-7}	1.82×10^{-5}	0.83	1.74×10^{-7}
High myopia	361 (6.12)	210 (9.81)	85 (4.44)	66 (3.59)	3.23×10^{-18}	8.07×10^{-11}	9.43×10^{-15}	0.55
Moderate myopia	373 (6.33)	205 (9.57)	99 (5.18)	69 (3.75)	2.09×10^{-14}	2.69×10^{-7}	4.54×10^{-13}	0.12
Low myopia	1386 (23.52)	572 (26.72)	410 (21.43)	404 (21.96)	6.44×10^{-5}	2.95×10^{-4}	1.54×10^{-3}	1
No myopia	3774 (64.03)	1154 (53.90)	1319 (68.95)	1301 (70.71)	1.54×10^{-33}	2.59×10^{-22}	2.84×10^{-27}	0.77
Education level, no. (%)								
No formal education	1107 (18.78)	367 (17.14)	276 (14.43)	464 (25.22)	1.24×10^{-17}	0.06	1.36×10^{-9}	2.41×10^{-16}
Primary education	2201 (37.34)	689 (32.18)	709 (37.06)	803 (43.64)	6.68×10^{-13}	3.54×10^{-3}	2.52×10^{-13}	1.09×10^{-4}
O or N levels	1491 (25.30)	586 (27.37)	469 (24.52)	436 (23.70)	0.02	0.12	0.03	1
A levels, polytechnic, diploma, certification	637 (10.81)	290 (13.55)	225 (11.76)	122 (6.63)	6.27×10^{-12}	0.27	1.69×10^{-12}	1.63×10^{-7}
University education	451 (7.65)	209 (9.76)	230 (12.02)	12 (0.65)	1.53×10^{-42}	0.068	5.32×10^{-43}	5.56×10^{-54}
Others	5 (0.08)	0 (0)	4 (0.21)	1 (0.05)	0.06	—	—	—

D = diopter; MMD = myopic macular degeneration; SD = standard deviation; SE = spherical equivalent; — = not applicable.
The Singapore Epidemiology of Eye Diseases comprises 5894 unrelated individuals with both phenotype and genotype data after quality control.
*The Kruskal-Wallis test was used to test for global differences in continuous phenotype across the 3 ancestries. The chi-square test was used to test global differences in counts across the 3 ancestries. The counts in each myopia group were compared with the remaining individuals (e.g., MMD vs. no MMD, high myopia vs. no high myopia, etc.). Similarly, the counts in each education group were compared with the remaining individuals (e.g., university education vs. no university education).
†Pairwise comparisons were performed when the test for global differences was significant ($P_{global} < 0.05$). The pairwise comparison *P* values shown are adjusted for multiple comparisons using the Bonferroni method.

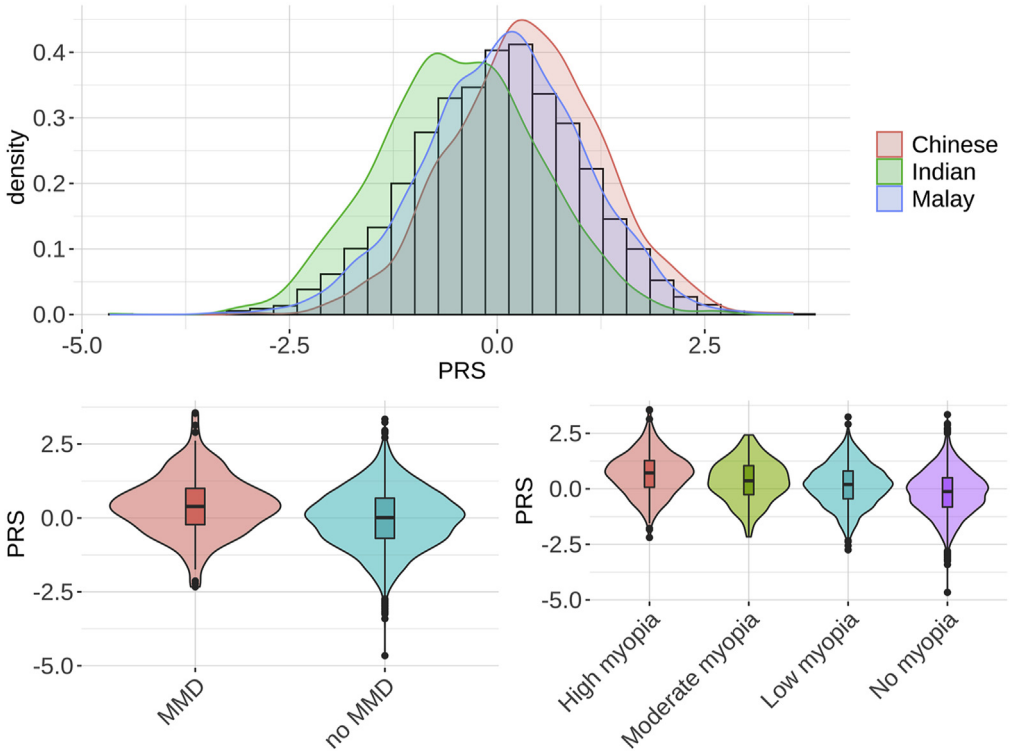

Figure 1. Graphs showing the distribution of the polygenic risk score (PRS) across ancestry and myopia groups in the Singapore Epidemiology of Eye Diseases (SEED) study. The PRS was significantly different across the 3 ancestries ($P = 9.27 \times 10^{-149}$) and increased with the degree of myopia, where high myopia corresponded to a higher PRS ($P = 3.44 \times 10^{-71}$). Individuals diagnosed with myopic macular degeneration (MMD) showed a significantly higher PRS as compared with individuals without MMD ($P = 2.36 \times 10^{-10}$).

separately, excluding ancestral outliers (12 Chinese, 177 Indian, and 46 Malay participants) within each group. The basic model explained between 2.80% (Malay participants) and 8.03% (Chinese participants) of SE variance and 8.38% (Malay participants) to 11.73% (Indian participants) of AL variance. Chinese participants showed the largest magnitude of PRS effect for both SE and AL (Fig 2). The variance explained by the PRS differed from 3.01% (95% CI, 1.47%–4.54%; $P = 5.26 \times 10^{-14}$, ANOVA) in Malay participants to 7.35% (95% CI, 5.02%–9.68%; $P = 2.58 \times 10^{-32}$, ANOVA) in Indian participants when the PRS was added to the basic model for SE. Similarly, the variance explained by the PRS differed from 1.83% (95% CI, 0.62%–3.04%; $P = 1.42 \times 10^{-9}$, ANOVA) in Malay participants to 4.77% (95% CI, 3.02%–6.51%; $P = 4.94 \times 10^{-27}$, ANOVA) in Chinese participants when the PRS was added to the basic model for AL (Fig 3).

We tested the robustness of the results by including EA and an EA-by-ancestry interaction as covariates to the basic model to capture nongenetic effects. The basic model with the inclusion of EA and EA-by-ancestry interaction explained 13.80% and 19.24% of SE and AL variance, respectively. Adding the PRS to this model showed that the PRS explained 4.88% (95% CI, 3.81%–5.94%; $P = 2.06 \times 10^{-76}$, ANOVA) and 3.16% (95% CI, 2.29%–4.04%; $P = 5.20 \times 10^{-53}$, ANOVA) of the SE and AL variance, respectively, with approximately 2 orders of magnitude stronger PRS-association P values.

Prediction Performance of the Polygenic Risk Score on High Myopia

Figure 4 illustrates the AUCs for HM. A basic model with age, sex, EA, and ancestry; age-by-ancestry, sex-by-ancestry, and EA-by-ancestry interactions; and 20 genotypic PCs as covariates showed AUCs of 0.76 (95% CI, 0.73–0.79) for HM versus no HM and 0.79 (95% CI, 0.77–0.82) for HM versus no myopia. When only the PRS was in the model, the AUCs were 0.70 (95% CI,

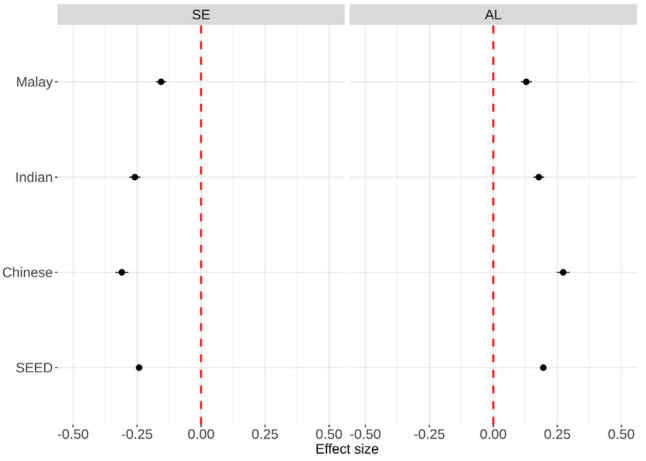

Figure 2. Graph showing the polygenic risk score (PRS) association effect sizes for spherical equivalent (SE) and axial length (AL; in the worse eye). The PRS was tested in 5894 unrelated individuals in the Singapore Epidemiology of Eye Diseases (SEED) study (2141 Chinese, 1913 Indian, and 1840 Malay participants). Ancestry-stratified analysis excluded 12 Chinese participants, 177 Indian participants, and 46 Malay participants as ancestral outliers. Points represent association effect estimates. Error bars represent standard errors. The red dashed line is a reference line at 0.

0.67−0.73, HM vs. no HM) and 0.73 (95% CI, 0.70−0.75, HM vs. no myopia). Adding the PRS to the basic model (i.e., basic covariates + PRS) showed AUCs of 0.80 (95% CI, 0.78−0.83; $P = 9.95 \times 10^{-8}$, DeLong's test) for HM versus no HM and 0.84 (95% CI, 0.82−0.86; $P = 2.77 \times 10^{-9}$, DeLong's test) for HM versus no myopia.

Individuals with a PRS in the upper percentiles showed an increased risk of HM versus control participants without myopia. For example, individuals in the top 50% of the PRS distribution showed 3.97 (95% CI, 3.08−5.16) times higher odds of having HM as compared with the remaining 50% of individuals, and those in the top 25% had 4.32 (95% CI, 3.46−5.40) times higher odds of HM, those in the top 10% had 4.60 (95% CI, 3.55−5.92) times higher odds of HM, and those in the top 5% had 4.66 (95% CI, 3.34−6.42) times higher odds of HM compared with the remaining individuals. A similar trend was observed for HM versus no HM (Fig 5).

Prediction Performance of the Polygenic Risk Score on Myopic Macular Degeneration

Figure 4 illustrates the AUCs for MMD. The basic model (age, sex, EA, and ancestry; age-by-ancestry, sex-by-ancestry, and EA-by-ancestry interactions; and 20 genotypic PCs as covariates) showed an AUC of 0.76 (95% CI, 0.72−0.79) for MMD versus no MMD and 0.76 (95% CI, 0.73−0.79) for MMD versus no myopia. When only the PRS was in the model, the AUCs were 0.62 (95% CI, 0.59−0.66) for MMD versus no MMD and 0.66 (95% CI, 0.63−0.70) for MMD versus no myopia. The inclusion of the PRS in the basic model (i.e., basic covariates + PRS) increased the AUC to 0.77 (95% CI, 0.75−0.80; $P = 1.82 \times 10^{-3}$, DeLong's test) for MMD versus no MMD and 0.79 (95% CI, 0.76−0.82; $P = 2.16 \times 10^{-4}$, DeLong's test) for MMD versus no myopia.

Individuals with PRS in the upper percentiles also showed an increased risk of MMD versus control participants without myopia. Individuals in the top 50% of the PRS distribution had 2.45 (95% CI, 1.85−3.27) times higher odds of MMD as compared with the remaining 50% of individuals, and those in the top 25% had 2.53 (95% CI, 1.94−3.30) times higher odds of MMD, those in the top 10% had 2.79 (95% CI, 2.00−3.83) times higher odds of MMD, and those in the top 5% had 3.43 (95% CI, 2.27−5.05) times higher odds of MMD compared with the remaining individuals. A similar trend was observed for MMD versus no MMD (Fig 5). A sensitivity analysis showed that the AUC results for HM and MMD were robust to imbalance between case and control groups (Supplemental material, available at www.aaojournal.org).

Discussion

Main Findings

In this study, we leveraged summary statistics from the largest GWAS of myopia to date to generate a PRS to predict HM as well as MMD in an adult Singapore Asian population. We fundamentally tested the hypothesis of whether European-derived PRSs can be useful for the identification of individuals who are likely to demonstrate HM in adulthood. We found that the PRS was a significant predictor of both SE and AL, explaining 5.09% and 3.31% of the phenotypic variance, respectively. The PRS effect sizes showed significant variation across the 3 ancestries in an ancestry-stratified analysis, with Chinese participants showing the largest

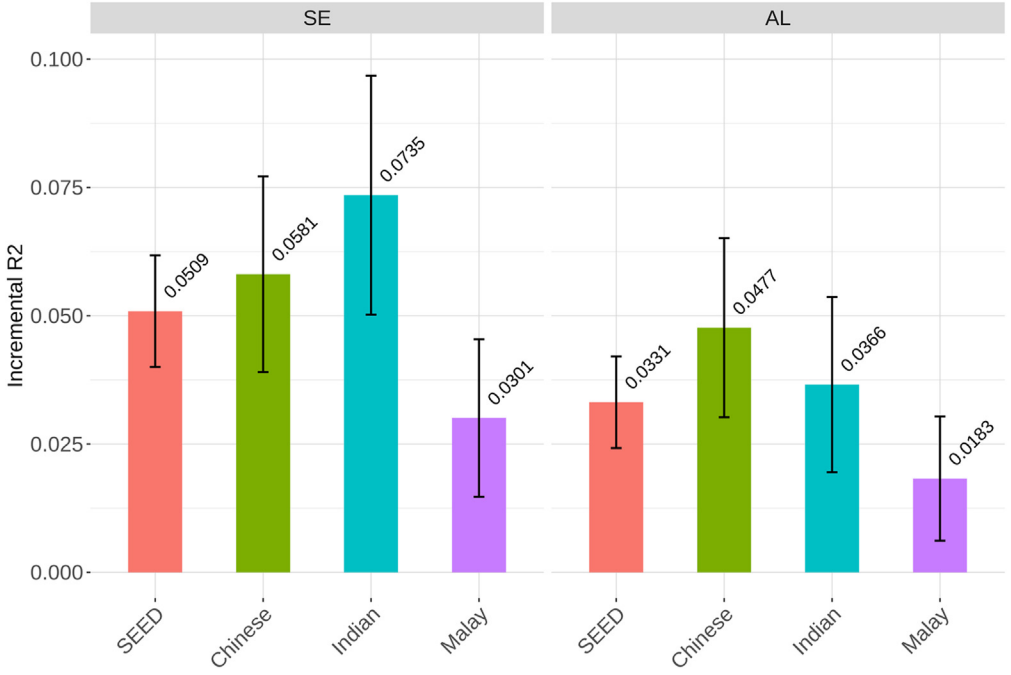

Figure 3. Bar graph showing the proportion of phenotypic variance explained by the polygenic risk score (PRS) for spherical equivalent (SE) and axial length (AL; in the worse eye). The PRS was tested in 5894 unrelated individuals in the Singapore Epidemiology of Eye Diseases (SEED) study (2141 Chinese, 1913 Indian, and 1840 Malay participants). Ancestry-stratified analysis excluded 12 Chinese participants, 177 Indian participants, and 46 Malay participants as ancestral outliers. The height of the bar represents the incremental R^2 value, or the gain in adjusted R^2 value when the PRS is added to the basic model. Error bars represent 95% confidence intervals.

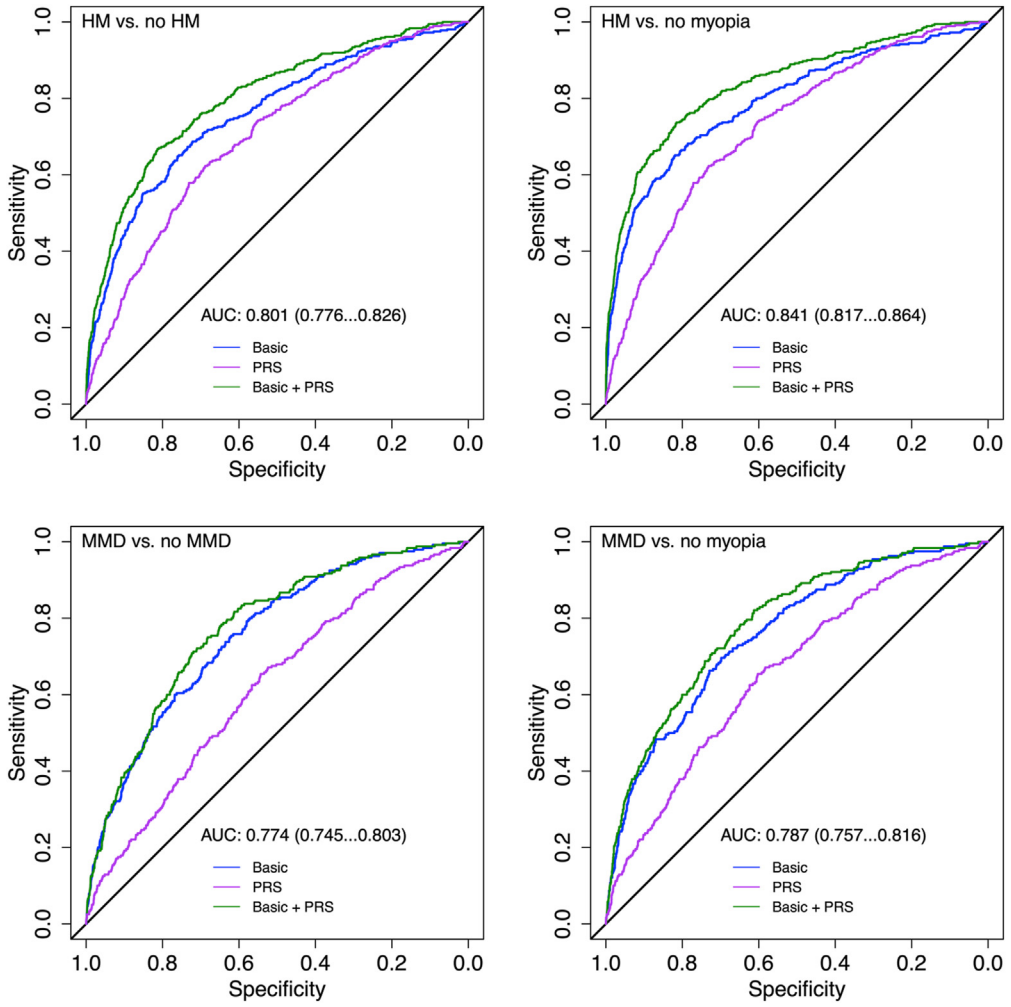

Figure 4. Receiver operating characteristic (ROC) curves and corresponding areas under the ROC curve (AUCs) were used to assess the ability of the polygenic risk score (PRS) to distinguish between high myopia (HM) and no HM and no myopia and between myopic macular degeneration (MMD) and no MMD and no myopia. The blue line is the ROC curve for a model with basic covariates (age, sex, educational attainment [EA], and ancestry; age-by-ancestry, sex-by-ancestry, and EA-by-ancestry interactions; and 20 genotypic principal components). The purple line is the ROC curve for a model with only the PRS. The green line is the ROC curve for a model with the PRS added to the basic model. The displayed AUC and corresponding 95% confidence interval are for the model corresponding to the green line (basic covariates + PRS).

magnitude of PRS effect. The highest prediction performance achieved was when the PRS was included in a model with age, sex, EA, and ancestry; age-by-ancestry, sex-by-ancestry, and EA-by-ancestry interactions; and 20 genotypic PCs (AUC, 0.84 for HM and 0.79 for MMD). Individuals in the upper percentiles of the PRS distribution were at increased risk of both HM and MMD. The most striking results indicate that individuals in the top 5% of the PRS distribution had up to 4.66 and 3.43 times higher odds of demonstrating HM and MMD, respectively, as compared with the remaining 95% of individuals. Our findings are a further confirmation that even nominally modest levels of explained quantitative trait variance can have relatively high predictive values. This known effect is explained by the differences between the heritability for quantitative traits and disease liability scale heritability.[40]

Polygenic Risk Score for High Myopia

The PRS provides a liability measure of the overall risk of an individual's genetic susceptibility to disease, which is an integral part of precision medicine.[15–17] The results of our study demonstrated that PRS could be a useful adjunctive clinical tool in identifying children with myopia at highest risk of HM developing, which is associated with higher rates of blindness and visual and quality of life impairment.[41]

The SE variance explained by the PRS (R^2 = 5.09%) in SEED was lower than that achieved by Ghorbani et al[23] in a similar analysis of Europeans (R^2 = 11.2%). Genetic prediction assumes that individuals in the discovery and test samples have the same genetic ancestry. Differences in the genetic architecture between the discovery (e.g., Europeans) and test (e.g., Singaporean Asians) samples can affect the transferability of PRS across diverse

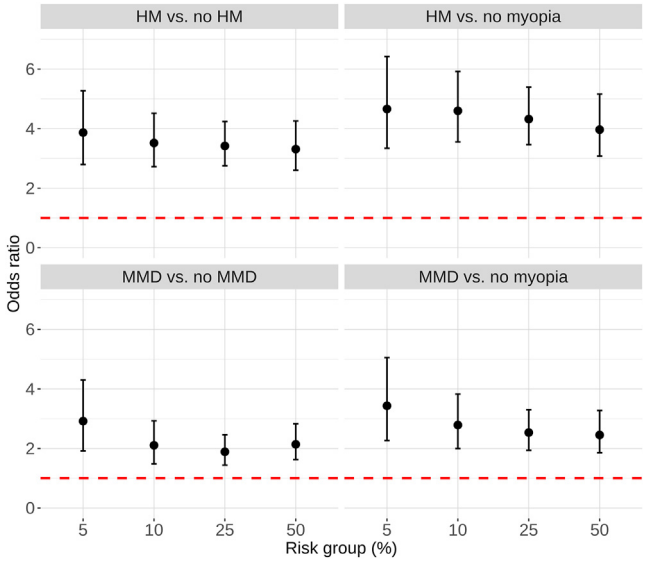

Figure 5. Graphs showing that individuals with a polygenic risk score (PRS) in the upper percentiles harbored an increased risk of myopia. Odds ratios were calculated by comparing those in the upper 5%, 10%, 25%, and 50% of the PRS distribution with the remaining individuals in the Singapore Epidemiology of Eye Diseases study (n = 5894). The red dashed line is the reference at unity. HM = high myopia; MMD = myopic macular degeneration.

populations. Empirical and theoretical studies have shown an expected decrease in prediction performance with greater genetic distance between the discovery and test samples.[42,43] Further, it has been demonstrated that prediction performance can vary with age, sex, and socioeconomic status, even when the discovery and test samples have similar genetic background.[44] In our benchmarking analysis (Supplementary Note 1), we found that the best-performing PRS for height, a model trait that is well powered for PRS analysis, explained $R^2 = 7.49\%$ of the phenotypic variance in SEED. Using a European discovery dataset, Wang et al[43] achieved a prediction $R^2 = 7.5\%$ in East Asians and $R^2 = 19.3\%$ in Europeans. Through theory and simulation, Wang et al demonstrated that the expected decrease in prediction performance for height in East Asians is 39.0% lower compared with Europeans, given the differences in the genetic architecture (e.g., differences in allele frequency and patterns of LD) between the 2 populations. The observed difference in prediction performance for height found by Wang et al is 38.9% ([0.075 / 0.193] × 100). Therefore, the lower R^2 value for SE in SEED versus that achieved by Ghorbani et al in Europeans (observed differences is [0.0509 / 0.112] × 100 = 45.4%) is expected because of differences in the genetic architecture (e.g., differences in heritability and a genetic correlation that deviates from unity[19]) of myopia between the 2 populations. Therefore, our results represent only a lower bound for the true predictive potential in Asian populations, and we expect that higher prediction performance will arise from a larger GWAS discovery cohort of Asian ancestry.

The PRS showed relatively low AUCs when considered as a single risk factor; however, the PRS should not be considered as an alternative to classical clinical risk models, but rather as an addition to aid in the diagnosis of myopia and the monitoring of myopia progression to HM, especially in the precision clinic setting. We anticipate that the myopia PRS will benefit clinical care in 4 key areas and will facilitate the development of clinical practice guidelines in eye care centers.[45] The first area is improvement in HM risk prediction for risk stratification. In contrast to classical (nongenetic) clinical risk factors (e.g., number of myopic parents, lifestyle factors such as time spend outdoors, etc.), the myopia PRS is constructed on the basis of inherited genetic variation, and therefore can be used early in life to estimate HM risk trajectories across lifetimes. Studies of coronary artery disease, for example, have shown that a prediction model that captures the effect of both classical clinical risk factors and a PRS has better prediction performance than a model with classical clinical risk factors alone.[46,47] The second area is enhancement of diagnostic accuracy. Diagnosis of HM is imperfect, and improvements in diagnostic accuracy with the aid of a myopia PRS can influence treatment plans and improve patient outcomes. For example, the polygenic nature and the frequency of myopia in the population indicates that it is possible for an individual to have a PRS in the upper percentile of the distribution with no known family history.[22] This is because of the between-family member genetic differences that occur as a result of random segregation of risk variants from parents to children at meiosis. Conversely, this also means that individuals may share fewer risk variants with their parents with myopia, and as a result have a relatively lower PRS. The third area is secondary prevention of disease progression in myopic children through treatment such as atropine eye drops and novel contact lenses. In childhood myopia, accurate early identification of high-risk children plays an important role in preventing irreversible globe elongation by enabling timely myopia control management. These interventions include topical atropine and multifocal lenses (e.g., myopic defocus spectacles and contact lenses),[48–54] which have been shown to be effective in arresting myopia progression. However, identifying children at risk of high myopia developing is often challenging in the clinical setting. Although high-risk features such as parental myopia,[9,55–57] childhood severity of myopia, age at onset of myopia, or environmental factors (near work and outdoor exposure)[13,57–60] are helpful, current childhood myopia management generally is based on 1 or 2 clinical parameters. Nevertheless, in early childhood, cycloplegia can be time consuming and HM high-risk features may not be predicted accurately based solely on family history of parental myopia and presenting cycloplegic refraction. Genetic prediction in specific cohorts where a higher prior probability of HM exists has the advantage of being applicable before myopia onset at very young ages by collecting saliva or buccal DNA in a noninvasive manner. The fourth area is augmentation in large-scale population screening. Population-level screening aims to identify individuals at high risk of HM

developing who may benefit from early intervention. In very young children, genetic testing could identify more accurately those who may require earlier screening and closer monitoring. The myopia PRS can be used as an objective adjunctive clinical tool to differentiate high-risk children for individualized myopia control treatment, which may justify early interventions or combination therapies to optimize myopia control outcomes. Although research evidence on the prophylactic use of myopia control treatment is still not available, time outdoors has been proven to be the best intervention so far to prevent myopia.[10] In specific cohorts where a higher prior probability of HM exists, the PRS also may help clinicians to recommend lifestyle changes, such as increasing outdoor time, that may benefit those at higher risk of HM (and who may not necessarily show symptoms at the time of examination) to slow or prevent progression to HM. Early low-risk intervention, such as increasing outdoor time, has been shown to alter the natural history of myopia, preventing an earlier myopia onset and ultimately improving quality of life in those children who avoid progression to HM in the latter teenage years and adulthood.

Polygenic Risk Score for Myopic Macular Degeneration

This study also examined the usefulness of the PRS to predict MMD. We showed that the PRS was able to distinguish individuals with MMD from control participants, although with lower prediction accuracy than for HM (e.g., the PRS alone had an AUC of 0.73 for HM vs. no myopia vs. an AUC of 0.66 for MMD vs. no myopia). The differences in prediction performance between HM and MMD indicate that differences may exist in the genetic and molecular mechanisms underlying MMD and HM and that MMD may be a more complex phenotype. This is consistent with previous genetic studies of MMD, which generally have been underpowered because of sample size, increased complexity of the MMD phenotype, or both.[26,27]

In adults with myopia, the PRS could be used to predict future development of MMD or for MMD risk stratification, which potentially is sight threatening.[61,62] It is one of the major causes of irreversible vision loss, accounting for 10 million individuals with visual impairment and 3.3 million individuals with blindness worldwide in 2015.[63–65] Moreover, individuals with MMD are at high risk for development of myopic choroidal neovascularization,[41,66,67] which is a treatable cause of vision loss with intravitreal anti−vascular endothelial growth factor therapy.[68] Because currently no established consensus for MMD screening protocol exists, the PRS potentially could be the solution to filling this gap. A key advantage of the PRS for MMD is the ability to identify those at higher risk of MMD for early screening of complications using ocular imaging, thereby avoiding late diagnosis with long periods of preclinical or asymptomatic disease. Individuals with high-risk of MMD developing may require surveillance to detect early signs of complications, and hence may benefit from timely interventions to avoid development of symptoms and irreversible pathologic features or visual impairment. Therefore, screening strategies using the PRS may be an effective measurement to minimize vision loss. The assessment by retinal or myopia specialists could include dilated fundus examination with ocular imaging such as OCT and OCT angiography if available, as they were found previously to be promising in identifying choriocapillaris changes in eyes with no or early MMD.[69] The PRS in the clinical setting ultimately will improve MMD risk stratification, screening, and clinical decision-making. The clinical scenario in which early intervention is introduced for patients at high risk of MMD developing based on PRS stratification may be an approach to alter the natural history of MMD by minimizing visual impairment. However, further studies are required to elucidate the relationship between the PRS and clinical features and treatment response in patients with MMD.

Study Limitations

This study has a few notable limitations. First, the study derived a myopia PRS for HM and MMD leveraging data from the largest GWAS of myopia in Europeans to date that is well powered for PRS analysis. However, as we noted previously, the heritability of myopia differs between Asians and Europeans, and a genetic correlation less than unity indicates some genome-wide differences in per-allele effect sizes between the 2 populations.[19] Therefore, a (expected) loss in predictive performance, as described above, ensues because of differences in the genetic architecture between the discovery and test populations. If we consider differences in LD, for example, the PRS aggregates the differences in LD between the discovery and test populations at individual SNPs along the genome that then contribute to overall differences in prediction performance, even if the causal variants and effects are shared between the 2 populations.[43,70] This was observed within the SEED cohort in the ancestry-stratified analysis, where the magnitude of PRS association effect size was larger in Chinese participants than in Indian and Malay participants. Second, this was a cross-sectional and not a longitudinal study, and ocular predictors such as age at onset of myopia or severity of myopia in childhood are not available. However, few studies have been conducted with a lifetime follow-up from childhood to adulthood. Third, we demonstrated that the myopia PRS was able to distinguish between individuals with MMD and control participants, although in general, the underlying genetics of MMD remain understudied and existing studies are underpowered,[26,27] indicating a need for more comprehensive studies of MMD. Further, the clinical application of the PRS for MMD currently is limited because few treatment options exist for adults considered to be at high risk for MMD. Nevertheless, we acknowledge that the most logical analysis is to develop a PRS specifically for MMD and to evaluate its predictive performance in SEED. However, this first would require a large-scale GWAS of MMD (in an

independent sample to avoid bias) to determine the association effect sizes (or weights) for the genome-wide variants included in the PRS. We postulate that a well-powered GWAS study of MMD (with similar genetic background to SEED) likely would provide higher predictive accuracy than one provided by the myopia PRS generated in this study; unfortunately, an underpowered MMD GWAS study would yield only effect estimates that are too imprecise for a clinically useful PRS. The next logical analysis (performed in this study) generated a myopia PRS and determined its ability to predict MMD. This analysis had 2 advantages: (1) the myopia PRS was generated from a large-scale GWAS of myopia[20] and was well powered for PRS analysis and (2) the observed differences in the predictive performance of the PRS for MMD and HM (as indicated by the lack of overlap of the AUC 95% CIs) suggests an underlying difference in the genetic architecture of the 2 phenotypes. This will inform future study designs of MMD and HM.

To address these limitations, future large-scale myopia (including HM and MMD) GWASs are needed in diverse Asian populations to examine the full predictive potential of the PRS on myopia and to further our understanding of the genetic and environmental mechanisms underlying myopia and myopia-related complications in Asians.

Conclusions

This study showed that genetic information can be used to predict the risk of HM and MMD development. We demonstrated the transancestry portability and usefulness of the PRS to stratify HM as well as MMD risk and presented key areas where the myopia PRS will benefit clinical care and will facilitate the development of clinical practice guidelines in eye care centers. Our findings help to further our understanding of the genetic mechanisms underlying HM and related complications such as MMD. Future large-scale myopia GWASs in diverse Asian populations are still needed.

Footnotes and Disclosures

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[1] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Republic of Singapore.

[2] Singapore Eye Research Institute, Singapore National Eye Centre, Singapore, Republic of Singapore.

[3] Duke-NUS Medical School, Singapore, Republic of Singapore.

[4] Escola Superior de Tecnologia da Saúde de Lisboa, Instituto Politécnico de Lisboa, Lisboa, Portugal.

[5] Comprehensive Health Research Center, Escola Nacional de Saúde Pública, Universidade Nova de Lisboa, Lisboa, Portugal.

[6] Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Republic of Singapore.

[7] Ophthalmology & Visual Sciences Academic Clinical Program, Duke-NUS Medical School, Singapore, Republic of Singapore.

[8] Section of Ophthalmology, School of Life Course Sciences, King's College London, London, United Kingdom.

[9] Department of Twin Research and Genetic Epidemiology, School of Life Course Sciences, King's College London, London, United Kingdom.

[10] UCL Great Ormond Street Hospital Institute of Child Health, University College London, London, United Kingdom.

[11] Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Republic of Singapore.

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No animal subjects were included in this study.

Author Contributions:

Conception and design: Hoang, Cheng, Saw

Analysis and interpretation: Kassam, Foo, Lanca, Xu, Hysi, Saw

Data collection: Hoang, Cheng, Saw

Obtained funding: Cheng, Saw

Overall responsibility: Kassam, Foo, Lanca, Hysi, Saw

Abbreviations and Acronyms:
AL = axial length; **ANOVA** = analysis of variance; **AUC** = area under the receiver operating characteristic curve; **CI** = confidence interval; **D** = diopter; **EA** = educational attainment; **GWAS** = genome-wide association study; **HM** = high myopia; **LD** = linkage disequilibrium; **MMD** = myopic macular degeneration; **PC** = principal component; **PRS** = polygenic risk score; **ROC** = receiver operating characteristic; **SD** = standard deviation; **SE** = spherical equivalent; **SEED** = Singapore Epidemiology of Eye Diseases; **SNP** = single nucleotide polymorphism.

Keywords:
High myopia, Multiethnic, Myopic macular degeneration, Polygenic risk score, Prediction.

Correspondence:
Seang-Mei Saw, PhD, Singapore Eye Research Institute, Singapore National Eye Centre, The Academia, 20 College Road, Discovery Tower Level 6, Singapore 169856, Singapore, Republic of Singapore. E-mail: ephssm@nus.edu.sg.

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