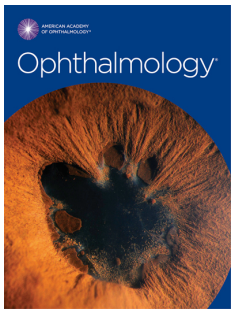

The potential of current polygenic risk scores to predict high myopia and myopic macular degeneration in multi-ethnic Singapore adults

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MAIN TABLES

Table 1: Summary statistics for Singapore Epidemiology of Eye Diseases (SEED) cohort. SEED is comprised of 5,894 unrelated individuals with both phenotype and genotype data after quality control.

						Pairwise comparisons^		
	SEED	**Chinese**	**Indians**	**Malays**	**P_{global}#**	**$P_{Chinese\_vs\_Indian}$**	**$P_{Chinese\_vs\_Malay}$**	**$P_{Indian\_vs\_Malay}$**
Sample size	5,894	2,141	1,913	1,840	--	--	--	--
Mean age (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}
Number of females (%)	2,894 (49.10)	1,048 (48.95)	918 (47.99)	928 (50.43)	0.32	--	--	--
Mean spherical equivalent in diopter (SD), worse eye	-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
Mean Axial length in mm (SD), worse eye	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, count (%)								
Myopic macular degeneration	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	1,386 (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	3,774 (64.03)	1,154 (53.90)	1,319 (68.95)	1,301 (70.71)	1.54×10^{-33}	2.59×10^{-22}	2.84×10^{-27}	0.77
Education, count (%)								
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/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/ITE/Cert	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	--	--	--

#Kruskal-Wallis test was used to test for global differences in continuous phenotype across the three ancestries. Chi-squares test was used to test global differences in counts across the three ancestries. The counts in each myopia group were compared to the remaining individuals (e.g. MMD vs. no MMD, HM vs. no HM, etc.). Similarly, the counts in each education group were compared to 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.

The potential of current polygenic risk scores to predict high myopia and myopic macular degeneration in multi-ethnic Singapore adults

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Running head: Polygenic risk score prediction of high myopia in Asians

Keywords: High myopia, myopic macular degeneration, polygenic risk score, prediction, multi-ethnic

ABSTRACT

Purpose

To evaluate the trans-ancestry portability of current myopia polygenic risk scores (PRS) to predict high myopia (HM) and myopic macular degeneration (MMD) in an Asian population.

Design

Population-based study.

Subjects

A total of 5,894 (2,141 Chinese, 1,913 Indians and 1,840 Malays) adults from the Singapore Epidemiology of Eye Diseases (SEED) study were included in the analysis. The mean age was 57.0 (standard deviation, SD = 9.31) years. A total of 361 adults had HM (spherical equivalent, SE <-5.00D) from refraction measurements, 240 individuals were diagnosed with MMD graded by the Meta-PM criteria from fundus photographs and 3,774 individuals were controls without myopia (SE >-0.5D).

Methods

The PRS, derived from 687,289 HapMap3 SNPs from the largest genome-wide association study of myopia in Europeans to-date (n = 260,974), was assessed on its ability to predict HM and MMD versus controls.

Main outcome measures

The primary outcomes were the area under the receiver operating characteristic curve

(AUROC) to predict HM and MMD.

Results

The PRS had an AUROC of 0.73 (95% CI: 0.70, 0.75) for HM and 0.66 (95% CI: 0.63, 0.70) for MMD versus no myopia controls. 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 AUROC 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% had 4.66 (95% CI: 3.34, 6.42) times higher risk for HM and 3.43 (95% CI: 2.27, 5.05) times higher risk for MMD compared to the remaining 95% of individuals.

Conclusion

The PRS is a good predictor for HM and will facilitate the identification of high-risk children to prevent myopia progression to HM. In addition, the PRS also predicts MMD and will help to identify high-risk myopic adults who require closer monitoring for myopia-related complications.

INTRODUCTION

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 where the risk increases with the degree of myopia. For example, each additional diopter (D) of myopia carries an increased risk of developing ocular complications such as myopic macular degeneration (MMD, 58%), retinal detachment (30%), posterior subcapsular cataract (21%) and open-angle glaucoma (20%)[5]. MMD 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 partially attributed 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 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 evenly distributed, the individual genetic profile may determine the relative disease risk within that population. One of the promises of precision medicine is the ability to accurately predict an individual's risk for common diseases from their DNA sequence[15–17]. Several large-scale genome-wide association studies (GWAS) 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 some differences in effect sizes[19]. The largest GWAS to-date has been conducted in Europeans and has 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, while 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) summarise 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 utility of the PRS to stratify myopia risk, though these studies have primarily 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. in Europeans[23], where 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 the majority of large-scale myopia GWAS primarily performed in individuals of European ancestry[18–21], it remains unclear if these findings are generalisable 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 teenage HM from no myopia controls with an area under the receiver operating characteristic curve (AUROC) 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 SNPs previously associated with high myopia for association with highly myopic cases with MMD (versus emmetropic controls or high myopic cases without MMD) in Europeans and Asians. Two significantly associated SNPs were identified in the *KCNMA1* gene and downstream from the *GJD2* gene for high myopic cases with MMD versus emmetropic controls, and none were identified when compared to high myopic cases without MMD, indicating limited power due to sample size and/or increased complexity in the MMD phenotype. Therefore, due to these limitations is power, few, if any, studies have examined the utility 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, comprised of unrelated Chinese (n=2,141), Indians (n=1,913) and Malays (n=1,840). We aimed to evaluate the trans-ancestry portability of the myopia PRS in an Asian population.

METHODS

The Singapore Epidemiology of Eye Diseases (SEED) dataset

SEED is a population-based study conducted in Singapore from 2004 to 2011. It is comprised of Chinese (recruitment conducted in 2009–2011), Indians (recruitment conducted in 2007–2009) and Malays (recruitment conducted in 2004–2006). Full study methodologies have

been described previously[28]. A total of 2,182 Chinese, 2,143 Indians and 2,105 Malays had both phenotype and genotype data available for analysis.

The study adhered to 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:

1) History of cataract surgery, aphakic or pseudophakic, and/or self-reported refractive surgery in both eyes.
2) Missing refraction data in both eyes.
3) Combination of cataract surgery in one eye and missing refraction data in the other eye.

Refraction and biometry measures

Individuals had a detailed ophthalmologic examination, where non-cycloplegic refraction status was determined using an autorefractor (model RK5; Canon, Tochigiken, Japan). Refraction was then subjectively refined until the best-corrected visual acuity was obtained. The results from subjective refraction were used in the analysis. SE of refractive error was defined as sphere plus half cylinder. Individuals were classified into myopia groups with myopia defined as individuals with SE≤−0.5D in at least one eye. Low (LM), moderate (MM),

and high (HM) myopia were defined as −3.0D<SE≤−0.5D, −5.0D<SE≤−3.0D, and SE≤−5.0D in the worse eye, respectively. AL was measured using non-contact partial coherence interferometry (IOL Master V.3.01; Carl Zeiss Meditec, Jena, Germany).

Grading of myopic macular degeneration

Colour fundus photographs centred on the optic disc and fovea were captured for each eye using standardised settings with a non-mydriatic retinal camera (Canon CR-DGi with 10D SLR back; Canon, Tokyo, Japan), after inducing cycloplegia. The photographs were graded using the International Photographic Classification and Grading System for Myopic Maculopathy (Meta-PM) protocol[29]. Based on fundus photograph grading, an eye was considered to have MMD if Meta-PM category 2 (diffuse chorioretinal atrophy), category 3 (patchy chorioretinal atrophy), category 4 (macular atrophy) or any 'plus' lesion, was observed[30]. The fundus photos were graded by one of two trained graders. Grading of pathological lesions by one retinal specialist and two trained graders were compared and there was high intergrader agreement (kappa coefficient = 0.92). All graders were masked to the subjects' characteristics.

Genotype imputation and quality control

Genotype data was 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 (Phase 3, Version 5) using the EAGLE2+Minimac3 pre-phasing and imputation pipeline[31]. Pre-imputation checks included ensuring all alleles are on the

forward strand, and coordinates and reference alleles are on the GRCh37 assembly. Pre-imputation quality control excluded autosomal genotyped SNPs with MAF <0.05, Hardy-Weinberg equilibrium (HWE) test P $<10^{-6}$, SNP missingness call rate >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 following imputation in each ancestry. Post-imputation quality control within each ancestry excluded imputed SNPs with MAF <0.05, HWE test P $<10^{-6}$, imputation info score <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 were in common between SEED and data from Hysi et al.[20], of which 796,522 are HapMap3 SNPs[33]. Autosomal genetic relationship matrices (GRMs) between individuals were calculated from the full set of imputed SNPs in each ancestry , separately, using the *–make-grm* command the GCTA 1.93 software package[34]. Unrelated individuals were identified with off-diagonal elements of the GRM <0.10 (i.e. equivalent to excluding approximately 3rd degree relatives or closer) using the *--grm-cutoff* command in GCTA within each ancestry. A total of 5,894 (2,141 Chinese, 1,913 Indians and 1,840 Malays) unrelated individuals in SEED remained and were included in downstream analyses.

Identifying ancestral outliers

Genetic ancestry for each individual in SEED was confirmed by multidimensional scaling (MDS) analysis (**Supplementary Figure S1**). Genotype data from SEED was combined with data from the 1000 Genomes (Phase 3) dataset comprised of 2,504 individuals from 26 populations. MDS analysis was performed on the combined set of individuals and 424,518

HapMap3 SNPs[33] that were filtered on MAF <0.05, HWE test P <10^{-6} and genotype call rate <0.01 using PLINK[32]. Ancestral outliers were defined as individuals more than three times the inter-quartile range (IQR) from the median of the first two MDS components. A total of 235 individuals (12 Chinese, 177 Indians and 46 Malays) 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**) 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. PRS for each individual, j, is defined as the weighted sum of SNP allele counts and can be written as,

$$PRS_j = \sum_{i=1}^{M} \hat{b}_i x_{ij} \quad (1)$$

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 using equation 6 from Zhu et al[35].

The myopia PRS was generated in each of the three ancestries in SEED using the SbayesS method implemented in the GCTB software[36], which performed best among six other approaches in our benchmarking analysis (**Supplementary Note 1**). SBayesS takes as input GWAS summary statistics and a 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**) 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 due to the complexity of this region using the *--exclude-mhc* command. MCMC chain was performed with 50,000 iterations (*--chain-length 50,000*), 20,000 burn in (*--burn-in 20,000*) and frequency of 10 (*--out-freq 10*). The number of chains was set to 4 (*--num-chains 4*). PRS was calculated for each individual in SEED by multiplying the best guess genotypes for 687,289 HapMap3 SNPs in common with SEED, Hysi et al[20] and the LD reference panel by the effect sizes reweighted by SBayesS using the PLINK *--score* function[32]. The PRS scores were then standardised to have mean zero and variance one. 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 three ancestries and myopia groups. The association between SE and AL (in the worse eye) and the PRS was tested in SEED using multivariable linear regression. All continuous phenotypes were standardised to have mean zero and variance one. The model can be written as,

$$\boldsymbol{y} = \boldsymbol{\mu} + \sum_{\boldsymbol{i=1}}^{\boldsymbol{T}} \boldsymbol{\beta_i x_i} + \boldsymbol{\beta}_{\mathbf{PRS}}\mathbf{PRS} + \boldsymbol{e} \quad (2)$$

where $\boldsymbol{y}$ is an n x 1 vector of SE or AL values, with sample size n; $\boldsymbol{\mu}$ is the intercept; $\boldsymbol{\beta_i}$ is fixed effect estimate for the $\boldsymbol{i^{th}}$ basic covariate, $\boldsymbol{x_i}$; $\boldsymbol{\beta}_{\mathbf{PRS}}$ is the fixed effect estimate for the **PRS**; and $\boldsymbol{e}$ is the residual. The $\boldsymbol{T}$ basic covariates included age, sex, ancestry, age- and sex-by-ancestry interactions and 20 genotypic principal components (PCs) derived from the GRM using the *–pca* command GCTA[34]. Height and height-by-ancestry interaction was additionally included as basic covariates for AL. Significance of the PRS was assessed with a one 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 units), standard error, 95% confidence interval (CI), association P-value and the incremental R^2 were used to assess the strength of associations. Incremental R^2 (hereafter referred to as R^2) was defined as the gain in adjusted R^2 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 two degrees-of-freedom ANOVA by comparing the interaction model to the model in Equation 2. The robustness of the results was tested by including educational attainment (EA) and an EA-by-ancestry interaction to the set of basic covariates in order to capture non-genetic effects. EA was treated as a categorical variable with five levels: no formal education (n = 1,107), primary education (n = 2,201), O/N levels (n = 1,491), A

levels/Polytechnic/Diploma/ITE/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 PRS on HM and MMD

The receiver operating characteristic (ROC) curve and the corresponding area under the curve (AUROC) was used to assess the ability of the PRS to distinguish between individuals with HM versus no HM and no myopia controls, and MMD versus no MMD and no myopia controls. The AUROC relates the false-positive rate (specificity) with the true-positive rate (sensitivity), and takes on values between 0.5 and 1, which represents a PRS with no and perfect discriminatory power, respectively. Logistic regression was performed on a binary variable (i.e. HM or MMD status versus controls) 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 3.6.0. A total of three 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 3.6.0 was then used to assess the ROC and AUROC. DeLong's test implemented in the *roc.test* command from the *pROC* library in R 3.6.0 was used to compare the AUROC between ROC curves from the nested models. In particular, model 3 (basic covariates + PRS) was compared against model 1 (basic covariates) in order to assess the significance of adding the PRS to the basic model. To determine if the AUROC estimates were robust to imbalance

between the myopia cases and control groups, we down-sampled control groups by randomly selecting individuals in the control group to match the number of samples in the cases group and estimated the AUROC. This was performed 1,000 times. Finally, odds ratios were calculated for individuals in the top 5^{th}, 10^{th}, 25^{th} and 50^{th} percentiles of the PRS distribution versus the remaining individuals. P-values were calculated with a chi-square test from the 2 x 2 table of myopia status versus PRS-risk group using the *oddsratio* command implemented in the *epitools* library in R 3.6.0.

URLs

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., https://cnsgenomics.com/software/gctb/#Download
6. GWAS summary statistics from Hysi et al., ftp://twinr-ftp.kcl.ac.uk/Refractive_Error_MetaAnalysis_2020
7. GWAS summary statistics from Jiang et al., https://yanglab.westlake.edu.cn/resources/fastgwa_data/UKB/50.v1.1.fastGWA.gz

RESULTS

Study participants

A total of 5,894 (2,141 Chinese, 1,913 Indians and 1,840 Malays) unrelated adults in SEED with both phenotype and genotype data were available for analysis after quality control. The mean age in SEED was 57.0 (standard deviation, SD = 9.31) years, and was significantly different across the three ancestries ($P = 4.55 \times 10^{-11}$), ranging from 55.83 (SD = 8.76) years in Indians to 57.86 (SD = 10.40) years in Malays. The proportion of females was 49% (P = 0.32). The mean SE was -0.53D (SD = 2.48), differing from -1.07D (SD = 2.87) in Chinese to -0.21D (SD = 2.27) in Indians ($P = 8.87 \times 10^{-29}$). Similarly, the mean AL was 23.72mm (SD = 1.25), varying from 23.45mm (SD = 1.11) in Indians to 24.05mm (SD = 1.41) in Chinese ($P = 1.73 \times 10^{-51}$). The proportion of individuals with no myopia was highest in Malays (70.71%), and the proportion of individuals with low (26.72%), moderate (9.57%) and high myopia (9.81%) was highest in Chinese. MMD diagnosis was highest in Malays (5.43%) as compared to Chinese (4.67%) and Indians (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 three ancestries ($P = 9.27 \times 10^{-149}$), with Chinese, on average, showing a higher PRS as compared to Indians and Malays. 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 had a higher PRS, on average, as compared to those without ($P = 2.36 \times 10^{-10}$).

Accuracy of the PRS for prediction of SE and AL

A basic model including age, sex, ancestry, age- and sex-by-ancestry interactions and 20 genotypic PCs as covariates (height and height-by-ancestry interaction were additionally 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 (**Figure 2**), with 5.09% (95% CI: 4.00%, 6.18%; ANOVA P = 1.62×10^{-74}) of SE variance explained by the PRS (**Figure 3**). Similarly, higher PRS was associated with longer AL, with 3.31% (95% CI: 2.42%, 4.21%; ANOVA P = 1.38×10^{-51}) of AL variance explained by the PRS. A significant interaction was observed between the PRS and ancestry for both SE (ANOVA P = 3.25×10^{-7}) and AL (ANOVA P = 3.59×10^{-6}), indicating variation in PRS effect sizes across the three ancestries. To investigate this further, we performed a stratified analysis in each ancestry, separately, excluding ancestral outliers (12 Chinese, 177 Indians and 46 Malays) within each group. The basic model explained between 2.80% (Malays) and 8.03% (Chinese) of SE variance, and 8.38% (Malays) to 11.73% (Indians) of AL variance. Chinese showed the largest magnitude of PRS effect for both SE and AL (**Figure 2**). The variance explained by the PRS differed from 3.01% (95% CI: 1.47%, 4.54%; ANOVA P = 5.26×10^{-14}) in Malays to 7.35% (95% CI: 5.02%, 9.68%; ANOVA P = 2.58×10^{-32}) in Indians 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%; ANOVA P = 1.42×10^{-9}) in Malays to 4.77% (95% CI: 3.02%, 6.51%; ANOVA P = 4.94×10^{-27}) in Chinese when the PRS was added to the basic model for AL (**Figure 3**).

We tested the robustness of the results by including EA and an EA-by-ancestry interaction as covariates to the basic model in order to capture non-genetic 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%; ANOVA P = 2.06×10^{-76}) and 3.16% (95% CI: 2.29%, 4.04%; ANOVA P = 5.20×10^{-53}) of the SE and AL variance, respectively, with approximately two orders of magnitude stronger PRS association P-values.

Prediction performance of the PRS on high myopia

Figure 4 illustrates the AUROCs 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 had AUROC of 0.76 (95% CI: 0.73, 0.79) for HM vs. no HM and 0.79 (95% CI: 0.77, 0.82) for HM vs. no myopia. When only the PRS was in the model, the AUROCs were 0.70 (95% CI: 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) had AUROC of 0.80 (95% CI: 0.78, 0.83; DeLong's test P = 9.95×10^{-8}) for HM vs. no HM and 0.84 (95% CI: 0.82, 0.86; DeLong's test P = 2.77×10^{-9}) for HM vs. no myopia.

Individuals with PRS in the upper percentiles had an increased risk of HM vs. no myopia controls. For example, individuals in the top 50% of the PRS distribution had 3.97 (95% CI: 3.08, 5.16) times higher odds of HM as compared the remaining 50% of individuals, and those in the top 25% had 4.32 (95% CI: 3.46, 5.40) times, top 10% had 4.60 (95% CI: 3.55, 5.92) times and top 5% had 4.66 (95% CI: 3.34, 6.42) times higher odds of HM compared to the remaining individuals. A similar trend was observed for HM vs. no HM (**Figure 5**).

Prediction performance of the PRS on myopic macular degeneration

Figure 4 illustrates the AUROCs 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) had AUROC of 0.76 (95% CI: 0.72, 0.79) for MMD vs. no MMD and 0.76 (95% CI: 0.73, 0.79) for MMD vs. no myopia. When only the PRS was in the model the AUROCs were 0.62 (95% CI: 0.59, 0.66) for MMD vs. no MMD) and 0.66 (95% CI: 0.63, 0.70; MMD vs. no myopia). The inclusion of the PRS in the basic model (i.e. basic covariates + PRS) increased the AUROC to 0.77 (95% CI: 0.75, 0.80; DeLong's test $P = 1.82 \times 10^{-3}$) for MMD vs. no MMD and 0.79 (95% CI: 0.76, 0.82; DeLong's test $P = 2.16 \times 10^{-4}$) for MMD vs. no myopia.

Individuals with PRS in the upper percentiles also showed an increased risk of MMD vs. no myopia controls. 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 the remaining 50% of individuals, and those in the top 25% had 2.53 (95% CI: 1.94, 3.30) times, top 10% had 2.79 (95% CI: 2.00, 3.83) times and top 5% had 3.43 (95% CI: 2.27, 5.05) times higher odds of MMD compared to the remaining individuals. A similar trend was observed for MMD vs. no MMD (**Figure 5**).

A sensitivity analysis showed that the AUROC results for HM and MMD were robust to imbalance between cases and control groups (see **Supplementary Note 2**).

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 PRS can be useful for the identification of individual who are likely to develop high myopia 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 three ancestries in an ancestry-stratified analysis, with Chinese showing the largest 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 (AUROC of 0.84 for HM and 0.79 for MMD). Individuals in the upper percentiles of the PRS distribution were at increased risk for both HM as well as MMD. The most striking result indicates that individuals in the top 5% of the PRS distribution had up to 4.66- and 3.43-times higher odds of HM and MMD, respectively, as compared to 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[39].

PRS for high myopia

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 myopic

children at highest risk for developing HM, which is associated with higher rates of blindness, visual and quality of life impairment[40].

The SE variance explained by the PRS (R^2 = 5.09%) in SEED was lower than that achieved by Ghorbani et al. in a similar analysis in Europeans (R^2 = 11.2%)[23]. 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 populations. Empirical and theoretical studies have shown that there is an expected decrease in prediction performance with greater genetic distance between the discovery and test samples[41,42]. 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[43]. 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. achieved a prediction R^2 = 7.5% in East Asians and R^2 = 19.3% in Europeans[42]. Through theory and simulation, Wang et al. demonstrate that the expected decrease in prediction performance for height in East Asians is 39.0% lower compared to Europeans given the differences in the genetic architecture between the two populations. The observed difference in prediction performance for height in Wang et al is 38.9% ([0.075/0.193] x 100). Therefore, the lower R^2 for SE in SEED versus that achieved by Ghorbani et al. in Europeans (observed differences is [0.0509/0.112] x 100 = 45.4%) is expected due to difference in the genetic architecture (e.g., differences in heritability and a genetic correlation that deviates from unity[19]) of myopia between the two populations.

Therefore, our results represent only a lower bound for the true predictive potential in Asian populations, and we expect higher prediction performance will arise from larger GWAS discovery cohort of Asian ancestry.

The PRS had relatively low AUROCs when considered as a single risk factor; however, the PRS should not be considered as an alternative to classical clinical risk models but 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 four key areas and facilitate the development of clinical practice guidelines in eye care centres[44]. First, improvement in HM risk prediction for risk stratification. In contrast to classical (non-genetic) 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 can therefore be used early in life to estimate HM risk trajectories across lifetimes. Indeed, 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[45,46]. Second, 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 due to the between-family member genetic differences that occurs 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 myopic

parents, and as a result have a relatively lower PRS. Third, secondary prevention of disease progression in myopic children through treatment such as atropine eyedrops, 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)[47–53], which have been shown to be effective in arresting myopia progression. However, identifying children at risk of developing high myopia is often challenging in the clinical setting. While high-risk features such as parental myopia[9,54–56], childhood severity of myopia, age of onset of myopia or environmental factors (near work and outdoor exposure)[13,56–58] are helpful, current childhood myopia management is generally based on one or two clinical parameters. Nevertheless, in early childhood, cycloplegia can be time-consuming and HM high-risk features may not be accurately predicted based solely on family history of parental myopia and presenting cycloplegic refraction. Genetic prediction in specific cohorts where there is a higher prior probability of HM has the advantage of being applicable prior to myopia onset at very young ages by collecting saliva or buccal DNA in a non-invasive manner. Fourth, augmentation in large-scale population screening. Population-level screening aims to identify individuals at high-risk for developing HM who may benefit from early intervention. In very young children, genetic testing could more accurately identify those that 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 individualised myopia control treatment, which may justify early interventions or combination therapies to optimise 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

539 so far to prevent myopia[10]. In specific cohorts where there is a higher prior probability of
540 HM, the PRS may also help clinicians recommend lifestyle changes, such as increasing
541 outdoor time, that may benefit those at higher risk for HM (and may not necessarily show
542 symptoms at the time of examination) to slow or prevent progression to HM. Early low-risk
543 intervention, such as increasing outdoor time, has been shown to alter the natural history of
544 myopia preventing an earlier myopia onset and ultimately will improve quality of life of
545 those children avoiding progression to HM in latter teen years and adulthood.
546
547 **PRS for myopic macular degeneration**
548
549 This is, to the best of our knowledge, the first study to examine the utility of the PRS to
550 predict MMD. We showed that the PRS was able to distinguish individuals with MMD from
551 controls, though with lower prediction accuracy than for HM (e.g., the PRS alone had
552 AUROC of 0.73 for HM vs. no myopia versus 0.66 for MMD vs. no myopia). The differences
553 in prediction performance between HM and MMD indicates that there may be differences
554 in the genetic and molecular mechanisms underlying MMD and HM, and that MMD may be
555 a more complex phenotype. This is consistent with previous genetic studies of MMD, which
556 have generally been underpowered due to sample size and/or increased complexity of the
557 MMD phenotype[26,27].
558
559 In adults with myopia, the PRS could be employed to predict future development of MMD
560 or for MMD risk stratification, which can be potentially sight-threatening[60,61]. It is one of the
561 major causes of irreversible vision loss, accounting for 10 million individuals with visual
562 impairment and 3.3 million individuals with blindness worldwide in 2015[62–64]. Moreover,

individuals with MMD are at high risk for development of myopic choroidal neovascularisation[40,65,66], which is a treatable cause of vision loss with intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy[67]. Since there is currently no established consensus for MMD screening protocol, the PRS could potentially be the solution to fill this gap. A key advantage of the PRS for MMD, is the ability to identify those at higher MMD risk 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 developing MMD may require surveillance to detect early signs of complications and hence benefit from timely interventions to avoid development of symptoms and irreversible pathology or visual impairment. Therefore, screening strategies using the PRS may be an effective measure to minimize vision loss. The assessment by retinal or myopia specialists could include dilated fundus examination with ocular imaging such as ocular coherence tomography (OCT) and angiography (OCT-A) if available, as it was previously found to be promising in identifying choriocapillaris changes in eyes with no or early MMD[68]. The PRS in the clinical setting will ultimately serve to improve MMD risk stratification, screening, and clinical decision-making. The clinical scenario in which early intervention is introduced for patients at high risk for developing MMD 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, clinical features and treatment response in MMD patients.

Limitations

There are a few notable limitations of our study. First, our study derived a myopia PRS for HM and MMD leveraging data from 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 two populations[19]. Therefore, there is a (expected) loss in predictive performance, as described above, due to 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 as shared between the two populations[42,69]. This was observed within the SEED cohort in our ancestry-stratified analysis, where the magnitude of PRS association effect size was larger in Chinese than Indians and Malays. Second, this a cross-sectional and not a longitudinal study, and ocular predictors such as age of onset of myopia or severity of myopia in childhood are not available. However, there are few studies with a lifetime follow-up from childhood to adult. Third, we demonstrated that the myopia PRS was able to distinguish between individuals with MMD versus controls, though, in general, the underlying genetics of MMD are still understudied and existing studies are underpowered[26,27], indicating a need for more comprehensive studies of MMD. However, the clinical application of the PRS for MMD is currently limited as there are few treatment options for adults considered 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. This, however, would first 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) would likely provide higher predictive accuracy than one provided by the myopia PRS generated in this study; but unfortunately, an underpowered MMD GWAS study would only yield 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 two 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 AUROC 95% confidence intervals) suggests an underlying difference in the genetic architecture of the two phenotypes. This will inform future study designs of MMD and HM.

To address these limitations, future large-scale myopia (including HM and MMD) GWAS 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 demonstrate the trans-ancestry portability and utility of the PRS to stratify HM as well as MMD risk, and present key areas where the myopia PRS will benefit clinical care and facilitate the development of clinical practice guidelines in eye care centres. Our findings help further our understanding of the genetic mechanisms underlying HM and

related complications such as MMD. Future large-scale myopia GWAS in diverse Asian populations are still needed.

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FIGURE LEGENDS

Figure 1: The distribution of the PRS across ancestry and myopia groups in SEED. The PRS was significantly different across the three 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) had significantly higher PRS as compared to individuals without ($P = 2.36 \times 10^{-10}$).

Figure 2: The association between SE and AL (in the worse eye) and the PRS was tested in 5,894 unrelated individuals in SEED (2,141 Chinese, 1,913 Indians and 1,840 Malays). Ancestry-stratified analysis excluded 12 Chinese, 177 Indians and 46 Malays as ancestral outliers. Points represent association effect estimates. Error bars represent standard errors. Red dashed line is a reference line at zero.

Figure 3: The association between SE and AL (in the worse eye) and the PRS was tested in 5,894 unrelated individuals in SEED (2,141 Chinese, 1,913 Indians and 1,840 Malays). Ancestry-stratified analysis excluded 12 Chinese, 177 Indians and 46 Malays as ancestral outliers. The height of the bar represents the incremental R^2, or the gain in adjusted R^2 when the PRS is added to the basic model. Error bars represent 95% confidence intervals.

Figure 4: The receiver operating characteristic (ROC) curve and the corresponding area under the curve (AUROC) were used to assess the ability of the PRS to distinguish between high myopia (HM) from no HM and no myopia, and myopic macular degeneration (MMD) from no MMD and no myopia. Blue line is the ROC curve for a model with basic covariates (age, sex, EA, and ancestry; age-by-ancestry, sex-by-ancestry and EA-by-ancestry interactions; and 20 genotypic PCs). Purple line is the ROC curve for a model with only the PRS. Green line is the ROC curve for a model with the PRS added to the basic model. The displayed AUROC and corresponding 95% confidence interval are for the model corresponding to the green line (basic covariates + PRS).

Figure 5: Individuals with PRS in the upper percentiles had an increased risk of myopia. Odds ratios were calculated by comparing those in the upper 5%, 10%, 25% and 50% of the PRS distribution to the remaining individuals in SEED (n = 5,894). The red dashed line is the reference at unity.

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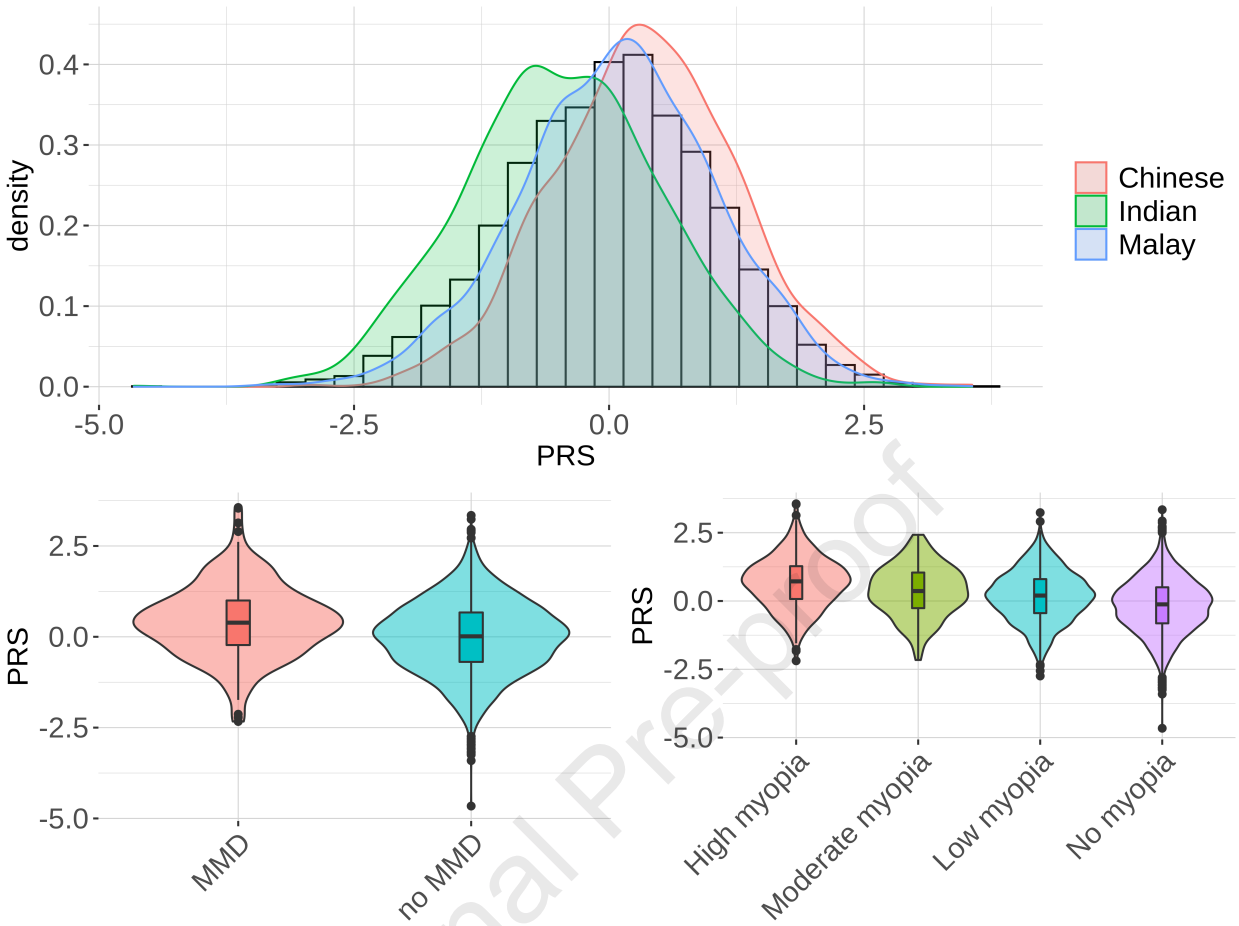

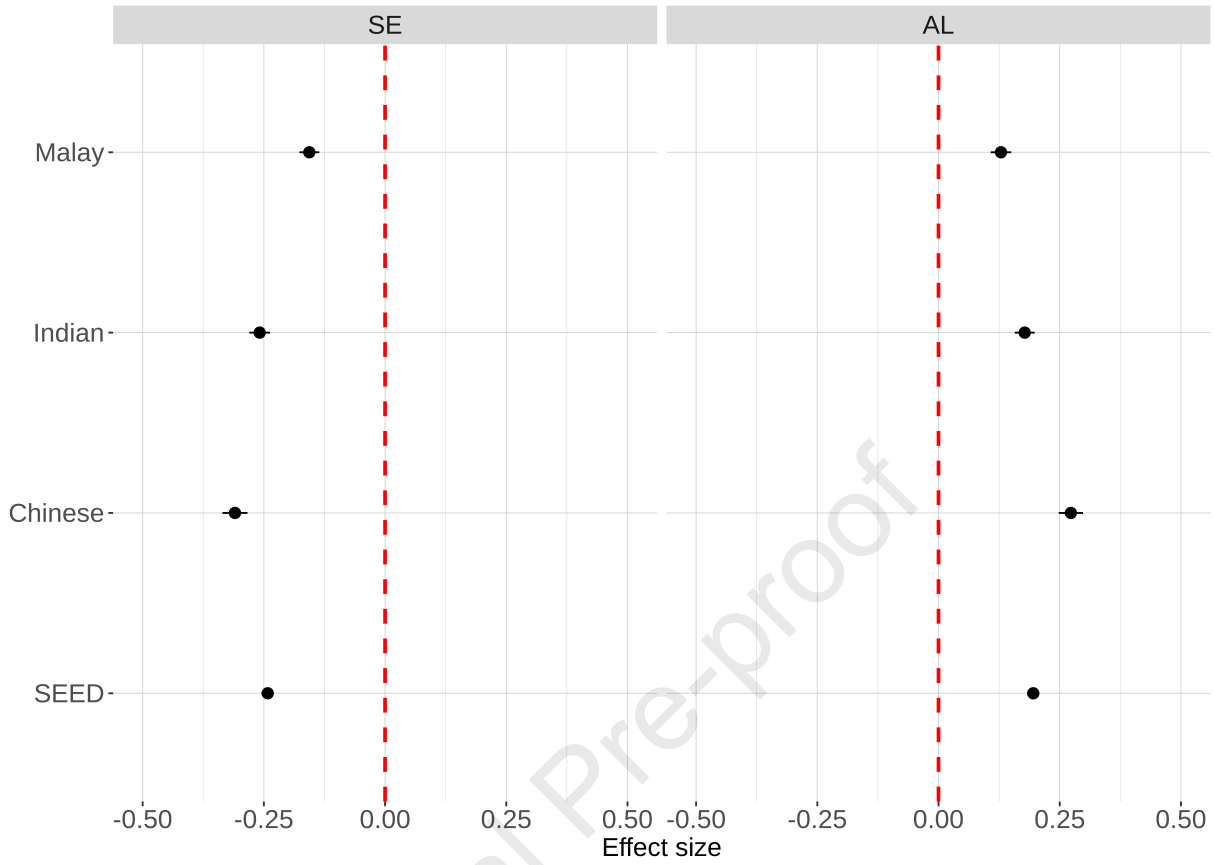

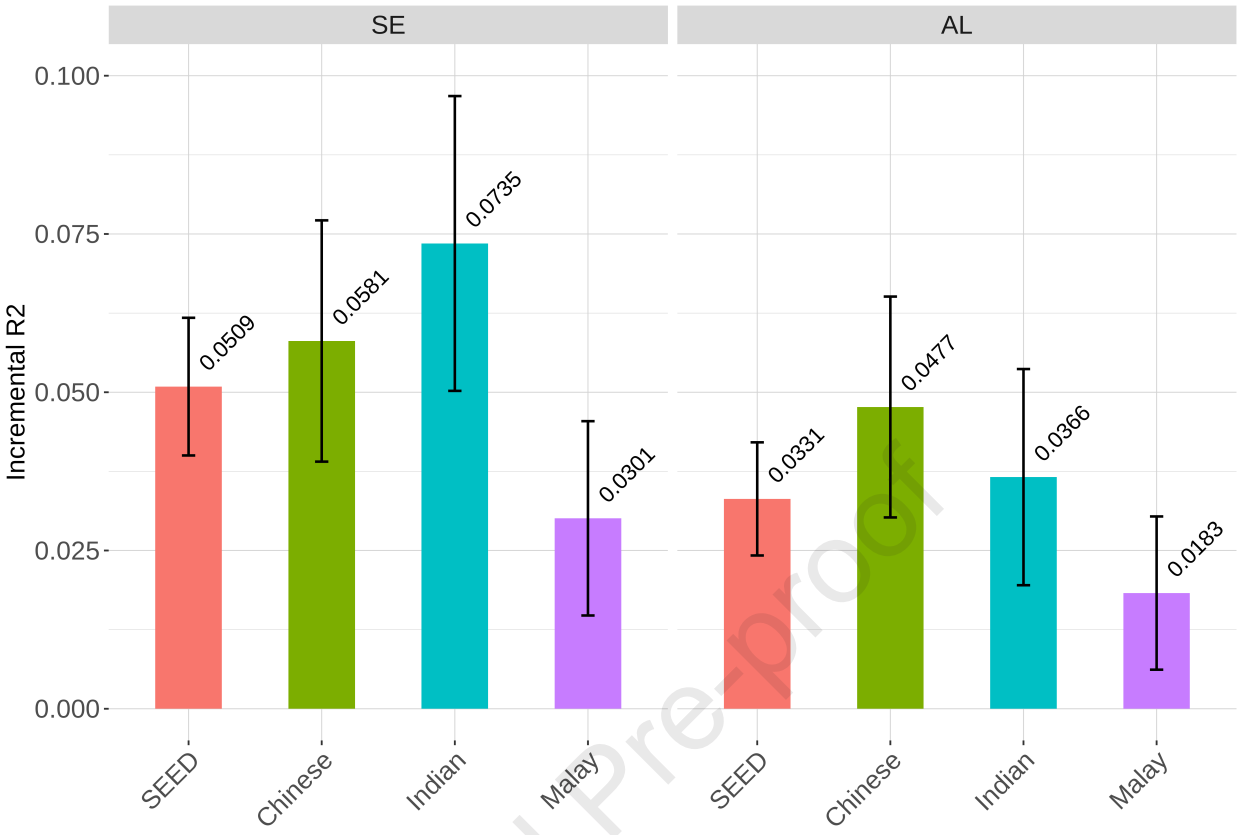

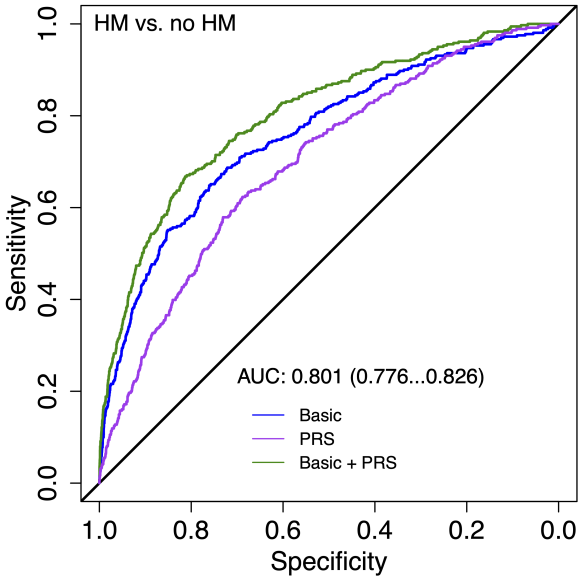

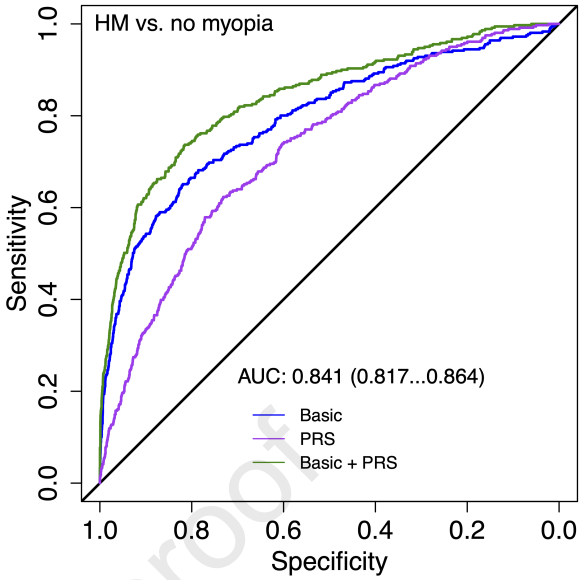

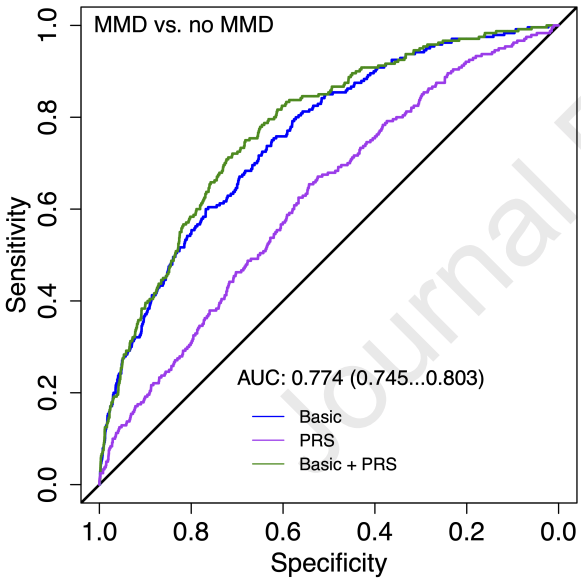

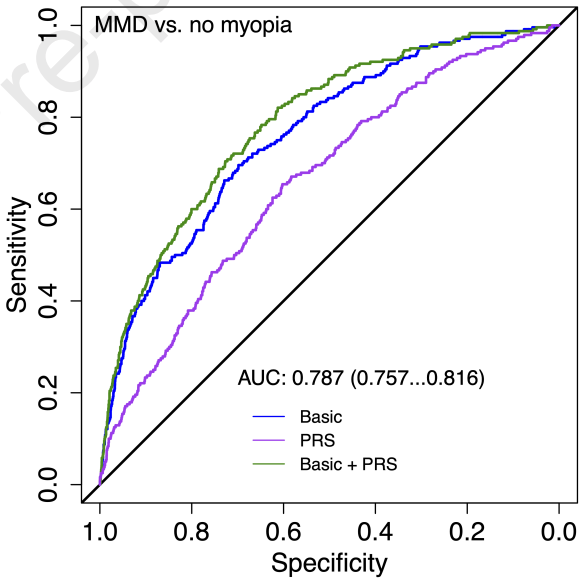

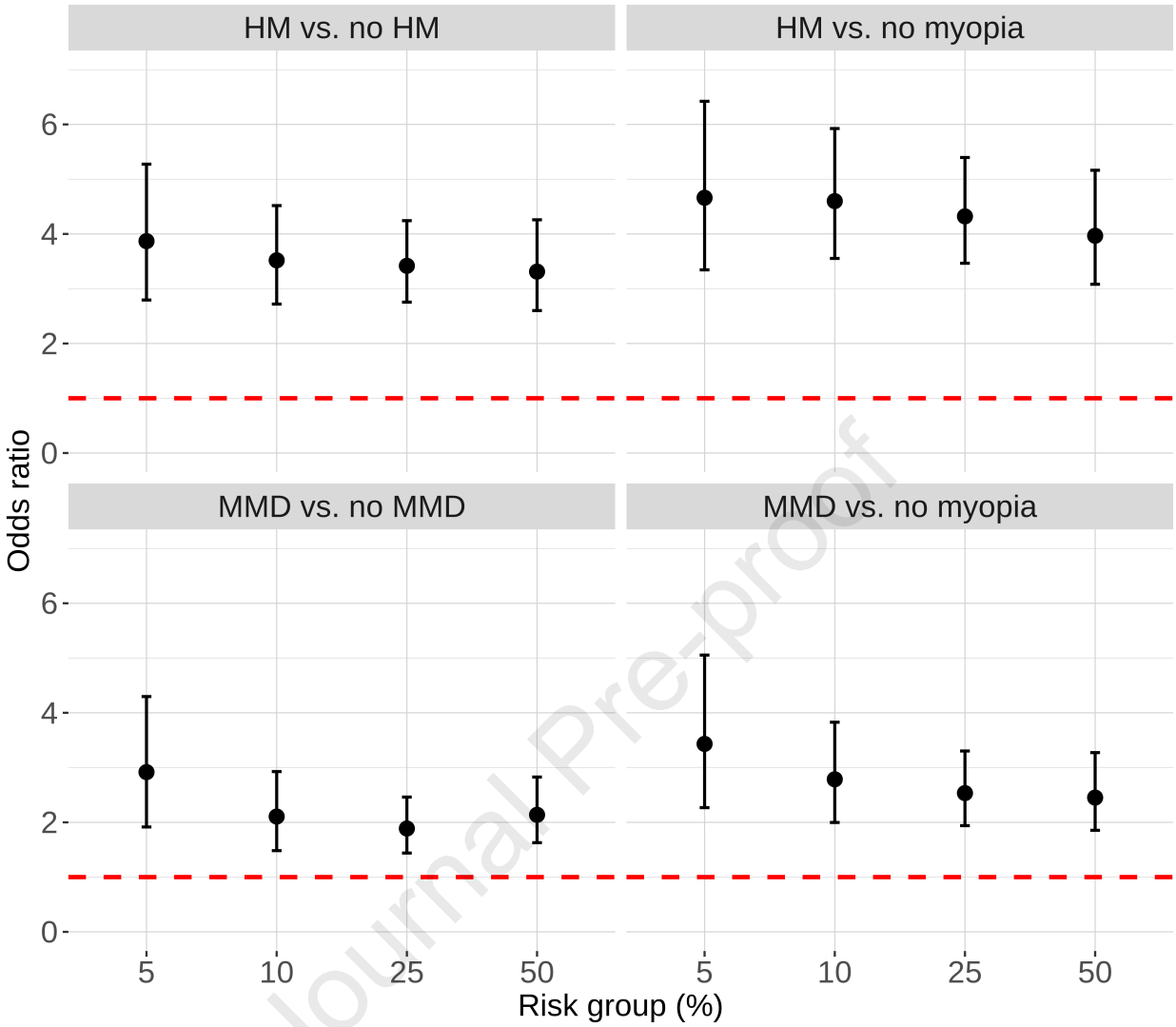

Précis [in 35 words]: Current myopia polygenic risk scores are good predictors of high myopia and myopic macular degeneration in Singapore Asian adults. Genetic risk profiling may be a useful tool to guide treatment and counselling decisions on myopia.