Determining Possible Shared Genetic Architecture Between Myopia and Primary Open-Angle Glaucoma

Adriana I. Iglesias,[1,2] Jue Sheng Ong,[3] Anthony P. Khawaja,[4,5] Puya Gharahkhani,[3] Milly S. Tedja,[1,6] Virginie J. M. Verhoeven,[1,2,6] Pieter W. M. Bonnemaijer,[1,6] Roger C. W. Wolfs,[2] Terri L. Young,[7] Nomdo M. Jansonius,[8] Jamie E. Craig,[9] Dwight Stambolian,[10] Cornelia M. van Duijn,[6,11,12] Stuart MacGregor,[3] and Caroline C. W. Klaver[1,6,13]; for the International Glaucoma Genetics Consortium (IGGC) and Consortium for Refractive Error and Myopia (CREAM)

[1]Department of Ophthalmology, Erasmus University Medical Center, Rotterdam, The Netherlands
[2]Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands
[3]Statistical Genetics, QIMR Berghofer Medical Research Institute, Brisbane, Australia
[4]National Institute for Health Research Biomedical Research Centre, Moorfields Eye Hospital National Health Service Foundation Trust and University College London Institute of Ophthalmology, London, United Kingdom
[5]Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom
[6]Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands
[7]Department of Ophthalmology and Visual Sciences, University of Wisconsin-Madison, Madison, Wisconsin, United States
[8]Department of Ophthalmology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[9]Department of Ophthalmology, Flinders University, Adelaide, Australia
[10]Department of Ophthalmology, University of Pennsylvania, Philadelphia, Pennsylvania, United States
[11]Leiden Academic Centre for Drug Research (LACDR), Leiden University, Leiden, The Netherlands
[12]Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom
[13]Department of Ophthalmology, Radboud University Medical Center, Nijmegen, The Netherlands

Correspondence: Caroline C. W. Klaver, Erasmus Medical Center, Room Na-2808, P.O. Box 2040, Rotterdam 3000 CA, The Netherlands; c.c.w.klaver@erasmusmc.nl.
Adrian I. Iglesias, Erasmus Medical Center, Wytemaweg 80, Rotterdam 3000 CA, The Netherlands; a.iglesiasgonzalez@erasmusmc.nl.

AII and JSO contributed equally to the work presented here and should therefore be regarded as equivalent first authors.

CMvD, SM, and CCWK contributed equally to the work presented here and should therefore be regarded as equivalent last authors.

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Purpose. To determine genetic correlations between common myopia and primary open-angle glaucoma (POAG).

Methods. We tested the association of myopia polygenic risk scores (PRSs) with POAG and POAG endophenotypes using two studies: the Australian & New Zealand Registry of Advanced Glaucoma (ANZRAG) study comprising 798 POAG cases with 1992 controls, and the Rotterdam Study (RS), a population-based study with 11,097 participants, in which intraocular pressure (IOP) and optic disc parameter measurements were catalogued. PRSs were derived from genome-wide association study meta-analyses conducted by the Consortium for Refractive Error and Myopia (CREAM) and 23andMe. In total, 12 PRSs were constructed and tested. Further, we explored the genetic correlation between myopia, POAG, and POAG endophenotypes by using the linkage disequilibrium score regression (LDSC) method.

Results. We did not find significant evidence for an association between PRS of myopia with POAG ($P = 0.81$), IOP ($P = 0.07$), vertical cup–disc ratio ($P = 0.42$), or cup area ($P = 0.25$). We observed a nominal association with retinal nerve fiber layer ($P = 7.7 \times 10^{-3}$) and a significant association between PRS for myopia and disc area ($P = 1.59 \times 10^{-9}$). Using the LDSC method, we found a genetic correlation only between myopia and disc area (genetic correlation [RhoG] $= -0.12$, $P = 1.8 \times 10^{-3}$), supporting the findings of the PRS approach.

Conclusions. Using two complementary approaches we found no evidence to support a genetic overlap between myopia and POAG; our results suggest that the comorbidity of these diseases is not influenced by common variants. The association between myopia and optic disc size is well known and validates this methodology.

Keywords: refractive error, primary open-angle glaucoma, polygenic risk score, genetic overlap

Myopia and primary open-angle glaucoma (POAG) are complex eye diseases in which both genetic and environmental factors play a role.[1,2] Myopia, or short-sightedness, is the most common form of refractive error, affecting approximately 1.4 billion people (approximately a quarter of the world population), expected to increase to 5 billion by 2050 (half of the world population).[3] By 2050, almost 1 billion people will be affected by high myopia,[3] the more severe form of myopia, which is commonly defined as a refractive error exceeding –6 diopters (D). POAG is a heterogeneous condition

characterized by progressive degeneration of the optic nerve that may lead to irreversible blindness, and is often associated with elevated intraocular pressure (IOP), the main modifiable risk factor in POAG development and progression.[4,5] It has been estimated that by 2020, between 53 and 65 million people will be affected by POAG.[6–8]

Although multiple epidemiologic studies have shown that patients with myopia, and particularly with high myopia (refractive error ≤ -6 D), have an increased risk of developing POAG among other ocular comorbidities,[9,10] there is conflicting evidence about the relation between myopia and glaucoma. On the one hand, various population-based studies have shown that the risk of developing glaucoma increases with the severity of myopia.[11–13] For example, a meta-analysis showed that the odds ratio (OR) of the association between glaucoma and low myopia (up to −3.00 D) is 1.65 (1.26–2.17), while the OR of the association between glaucoma and moderate-to-high myopia ($\leq$−3.00 D) is 2.46 (1.93–3.15).[11] On the other hand, other studies did not find any significant relation between myopia and POAG. The Ocular Hypertension Treatment Study did not find an association with POAG for either low ($<$−1.00 D), moderate (−1.00 to −3.00 D) or high myopia ($<$3.00 D)[4]; and in a population-based study, Weih et al.[12] reported an association between myopia ($\leq$0.5 D) and probable glaucoma but this association was no longer significant when only cases with definite glaucoma were analyzed. It is important to note that elongated myopic eyes (as observed in patients with high myopia) show anatomic and structural changes that are clinically very challenging to distinguish from those observed in POAG, which may lead to an overdiagnosis of POAG in myopic patients. Therefore, up until now, it is not clear whether myopia is truly a risk factor for glaucoma or not. Possible mechanisms and theories have been reported. Hypotheses include connective tissue vulnerability in the optic nerve of myopic individuals, anatomic changes in myopic eyes that associate with glaucomatous damage, and elongation of the ocular axis due to high IOP.[13]

Genome-wide association studies (GWAS) have identified 161 loci associated with common myopia,[14] 26 with POAG,[15–22] and more than 60 with quantitative traits or POAG endophenotypes, such as IOP, vertical cup–disc ratio (VCDR), and disc and cup area.[23] Although only one locus on chromosome 14 (close to the *SIX6* gene), has been consistently found to be associated with both myopia and POAG, other overlapping genomic regions have been identified between refractive error and POAG endophenotypes. Those regions include chromosome 20 close to the *BMP2* gene (refractive error and VCDR), chromosome 2 in proximity to the *EFEMP1* gene (refractive error and cup area), and chromosome 3 proximal to the *FNDC3B* gene (refractive error and IOP). To date, the genetic relationship between myopia and POAG has not been systematically studied.

Given the controversial relationship between both conditions and their polygenicity, we investigated whether common genetic variants associated with common nonsyndromic myopia underlie POAG and POAG endophenotypes. To accomplish this, we used two approaches. In the first approach, we constructed polygenic risk scores (PRSs) for myopia using the summary statistics from a meta-analysis of refractive error,[14] and then tested whether the myopia PRSs were associated with (1) POAG in 798 POAG cases and 1992 controls from the Australian & New Zealand Registry of Advanced Glaucoma (ANZRAG), and (2) with POAG endophenotypes (i.e., IOP, VCDR, cup and disc area) in 11,097 individuals from the Rotterdam Study (RS). As a second approach, we used summary statistics from the refractive error meta-analysis,[14] and POAG[17]/POAG endophenotypes[23] GWAS meta-analyses, to assess the genetic correlation between POAG and myopia using the linkage disequilibrium (LD) score regression method.[24]

Methods

Sample Description

This study includes data from two cohorts, ANZRAG and RS. Both adhered to the tenets of the Declaration of Helsinki and were approved by their local Medical Ethics Committees. All participants provided written informed consent.

The Australian & New Zealand Registry of Advanced Glaucoma (ANZRAG)

ANZRAG is a prospective study of POAG cases that aims to investigate genetic risk factors contributing to the development of glaucoma. The current study included 798 advanced POAG cases from ANZRAG and 1992 unscreened controls (drawn from the Australian Cancer Study or a study of inflammatory bowel diseases) who did not participate in the GWAS of refractive error conducted by the Consortium for Refractive Error and Myopia (CREAM). Cases and controls were drawn from Southern Adelaide Health Service/Flinders University, University of Tasmania, Queensland Institute of Medical Research, and the Royal Victorian Eye and Ear Hospital. Definition of advanced POAG in ANZRAG can be found in the Supplementary Materials. The patient DNA was genotyped on Illumina, Inc. (San Diego, CA, USA) Omni1M or Omni Express arrays. The quality control methods were performed in PLINK (http://www.cog-genomics.org/plink2/) by removing close relatives (i.e., pihat $>$ 0.2) with more than 3% missing genotypes, SNPs with call rate $<$ 97%, minor allele frequency (MAF) $<$ 0.01, and out of Hardy-Weinberg equilibrium (HWE), as described elsewhere.[17] Genotype imputation was performed using 1000 Genomes (http://www.internationalgenome.org/) Phase 1 Europeans as the reference panel. Additional details regarding genotype quality control and imputation can be found in Supplementary Table S1. All participants were Australians of European ancestry.

The Rotterdam Study (RS)

The RS is an ongoing prospective population-based study that aims to investigate determinants of disease occurrence and progression in the elderly.[25] In this study, data from the RS were used to investigate the association between PRSs for common, nonsyndromic myopia and quantitative traits of POAG, including IOP, VCDR, cup area, disc area, and retinal nerve fiber layer (RNFL). In brief, the RS started in 1990 and comprises 7983 subjects 55 years of age or over living in the Ommoord district in Rotterdam, The Netherlands. Participants underwent a home interview and an extensive ophthalmologic examination at baseline with follow-up examinations occurring every 3 to 4 years (RS-I). The cohort was further extended in 2000 (RS-II) and 2005 (RS-III), establishing a total of 14,926 participants. Of these, 11,097 have available data on POAG-related quantitative traits. The ophthalmologic assessment consisted of IOP measurements and optic nerve head assessment. In a subset of individuals ($n = 5261$), peripapillary RNFL was measured by optical coherence tomography (OCT). Details regarding phenotyping can be found in the Supplementary Data and Supplementary Table S2. Genotyping of SNPs was performed using the Illumina Infinium II HumanHap550 array (RS-I), the Illumina Infinium HumanHap 550-Duo array (RS-I, RS-II), and the Illumina Infinium Human 610-Quad array (RS-I, RS-III). Samples with low call rate ($<$97.5%), with

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excess autosomal heterozygosity (>0.336), or with sex mismatch were excluded, as were outliers identified by the identity-by-state (IBS) clustering analysis; outliers were defined as being >3 standard deviations (SD) from population mean or having IBS probabilities >97%. Further information on genotyping and imputation for both ANZRAG and RS is also provided in the Supplementary Table S1.

Calculation of PRS

PRSs of myopia were computed using the summary statistics from the GWAS meta-analysis conducted by CREAM and the personal genomics company 23andMe, Inc. (Mountain View, CA, USA) (combined $n = 160{,}420$).[14] Given that the RS was included in the CREAM meta-analysis, we used the summary statistics from the GWAS meta-analysis excluding RS-I, RS-II, and RS-III ($n = 10{,}775$). To calculate the PRS, we considered only autosomal variants with a high imputation quality (IMPUTE info score > 0.5 or minimac Rsq > 0.8) and a MAF > 1%. We then performed a *P* value-based clumping in PLINK excluding the MHC region and using an r^2 threshold of 0.2 and a physical distance threshold of 500 kb. This resulted in a total of 243,938 variants. In total, 12 scores were generated using the –score command in PLINK (v1.9) across strata of increasing liberal *P* value thresholds (score categories): 5.0×10^{-8}, 5.0×10^{-7}, 5.0×10^{-6}, 5.0×10^{-5}, 5.0×10^{-4}, 0.005, 0.01, 0.05, 0.1, 0.5, 0.8, and 1.0. The number of SNPs in each *P* value category can be found in Supplementary Table S3. For each individual in RS-I, RS-II, and RS-III ($n = 10{,}792$) and ANZRAG (n cases = 798 and n controls = 1992), 12 scores were calculated. Distribution of the PRS in each study can be found in Supplementary Figure S1, whereas the distribution of refractive error in the RS is shown in Supplementary Figure S2. To assess the predictive ability of the scores we tested the association of the constructed 12 PRSs for myopia with axial length (one of the major optical components of the eye) in the RS.

Statistical Analysis

Association of Myopia PRS With POAG. In order to evaluate whether PRS for myopia can explain variation in POAG susceptibility, we regressed the derived myopia PRS on the POAG outcome under a logistic model. The models were adjusted for sex and the first five ancestral principal components. The ANZRAG study was initially designed to ascertain glaucoma cases. Prior to our analyses, we excluded 358 ANZRAG participants who were included in the CREAM myopia GWAS meta-analysis to prevent bias in our estimates due to sampling overlap. The strength of the association between each of the 12 PRSs for myopia and POAG was assessed via the pseudo-R^2 (proportion of variance on POAG explained by myopia PRS) approach.

Association of Myopia PRS With POAG Quantitative Traits. We further assessed the association between the 12 PRSs for myopia with IOP ($n = 11{,}097$), three optic disc parameters to include VCDR ($n = 10{,}433$), cup area ($n = 10{,}404$) and disc area ($n = 10{,}418$), and RNFL measured by OCT ($n = 2215$) using linear regression. In total, 1.68% (187/11,097) of the participants from the RS received IOP-lowering medication (see Supplementary Table S4); in those individuals, we added 30% to the IOP measurement to estimate a premedication IOP value.[26] We excluded from the analysis those patients who underwent IOP-lowering laser or surgery. IOP and optic disc parameter analyses were corrected for age, sex, the first five principal components, and cohort. Disc area analyses were not corrected for eye size effect, as the main purpose of this study was to investigate whether there is an association between the PRSs for myopia and optic disc parameters. For the RNFL analysis, we excluded participants with age-related macular degeneration, cataract, aphakia, or pseudophakia, and scans with poor quality (i.e., image quality value < 45) as previously reported.[27] RNFL analyses were corrected for age, sex, the first five principal components, cohort, and OCT device, and an extra analysis including axial length was also performed. The proportion of variance explained by each PRS was calculated as the difference of R^2 in the full model as compared with the null model, which included the previously mentioned covariates but not the polygenic score. *P* values were determined from likelihood ratio tests, which compared the full model with the null model. Given the known relation between high myopia ≤ –6.00 D and POAG, we ran the same analyses in a subset of individuals of the RS with high myopia (≤–6.00 D, $n = 232$), and with moderate myopia (–5.99 to –3.00 D, $n = 771$). Given the limited number of participants with OCT data available, RNFL was not analyzed in the subgroup of individuals with high and moderate myopia. In the RS, we analyzed 12 PRSs in three subgroups (i.e., high myopia, moderate myopia, and all), and two categories of phenotypes (IOP and optic disc parameters). In addition, we tested whether the 12 PRSs were associated with RNFL in a subgroup of the RS with OCT data available, for a total of 84 tests in the RS. In ANZRAG we explored 12 PRSs. Hence, we set our Bonferroni-corrected threshold to 5.2×10^{-4} (0.05/96). All regression analyses in ANZRAG and RS were performed using the statistical package R (version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria).

LD Score Regression

Cross-trait LD score regression method was used to assess the genetic overlap between myopia and POAG, including POAG quantitative traits. GWAS summary statistics from the Europeans-only meta-analyses[14,23,17] were used to estimate genetic correlation between pairs of traits using the LD score regression program.[24,28] To restrict the analyses to well-imputed SNPs, we included only SNPs with MAF > 0.01 that were present in HapMap3. More details can be found in the Supplementary Materials. We set our Bonferroni-corrected threshold to 0.05/5 = 0.01 (correction for myopia versus POAG, VCDR, IOP, and cup and disc area).

Results

Table 1 shows the characteristics of both studies. We tested the ability of the calculated PRSs for myopia to predict axial length. The calculated PRSs for myopia explained up to 6.1% of the variance of axial length. We observed that the prediction accuracy demonstrated plateauing at a *P* value threshold of 0.5 (see Supplementary Table S5).

Polygenic Risk Score Analyses

Association of PRSs With POAG in the ANZRAG Study. Table 2 summarizes the association of myopia PRSs on POAG. None of the myopia PRSs were significantly associated with POAG. Our result showed that genetic predisposition on refractive error did not predict POAG status, as shown with the close-to-zero estimated pseudo-R^2 results for all PRS categories (R^2 range, 1.4×10^{-4}–2.0×10^{-5}).

Association of PRSs With POAG Endophenotypes in the Rotterdam Study. The association between PRSs for myopia and POAG endophenotypes is shown in Table 2. Among the POAG endophenotypes evaluated, the association between PRSs for myopia and disc area was the strongest

Table 1. Demographics and Ocular Characteristics in the ANZRAG and the Rotterdam Study

Study	*n*	% Men	Controls (Cases)	Cases With Missing Data	Mean (SD)	Age Range
Case–control study						
POAG age at diagnosis						
ANZRAG (excl. CREAM)	2790	40.30	1992 (798)	256	59 (14.2)	16–90
Intraocular pressure*						
ANZRAG	2790	40.30	1992 (798)	101	27 (10.4)	10–78
Study	***n***	**% Men**	**Mean (SD)**	**Range**	**Mean Age (SD)**	**Age Range**
Population-based study						
Intraocular pressure						
RS-I	6010	40.30	14.7 (3.2)	5.0–28.6	69.2 (9.0)	55–101
RS-II	2095	45.90	14.2 (3.1)	7.0–31.5	64.8 (7.9)	55–95
RS-III	2992	43.70	13.6 (2.9)	4.5–30.0	57.2 (6.8)	46–97
Vertical cup–disc ratio						
RS-I	5573	40.90	0.50 (0.13)	0.05–0.87	68.0 (8.4)	55–99
RS-II	1987	46.10	0.50 (0.13)	0.10–0.86	64.7 (7.7)	55–96
RS-III	2873	43.90	0.29 (0.21)	0.00–1.00	57.2 (6.6)	46–90
Cup area						
RS-I	5555	40.90	0.61 (0.34)	0.01–1.98	68.0 (8.4)	55–99
RS-II	1979	46.00	0.57 (0.32)	0.03–1.94	64.7 (7.7)	55–96
RS-III	2870	43.80	0.40 (0.30)	0.00–1.90	57.2 (6.6)	46–90
Disc area						
RS-I	5563	41.00	2.42 (0.47)	0.58–5.13	68.0 (8.4)	55–99
RS-II	1983	46.10	2.33 (0.46)	1.13–5.19	64.7 (7.7)	55–96
RS-III	2872	43.80	1.92 (0.40)	0.75–4.22	57.2 (6.6)	46–90

* Due to ANZRAG's cohort design, IOP measurements were estimated among cases only and were obtained prior to any treatment.

(highest R^2 0.27%, P value $= 1.6 \times 10^{-9}$). We found suggestive associations between PRSs for myopia and IOP with an average R^2 of 0.02%, although these associations were not significant after multiple testing adjustments (lowest P value = 0.01). Suggestive associations were also observed between PRSs for myopia and RNFL (Table 3) with an average R^2 of 0.13% (lowest P value $= 4.5 \times 10^{-3}$). To further investigate if the nominal association between PRSs for myopia and RNFL was driven by participants with glaucoma, we removed from the analyses individuals with glaucomatous visual field loss (GVFL), and observed that the results did not change (average R^2 of 0.14%, lowest P value $= 7.7 \times 10^{-3}$). None of these associations surpass our Bonferroni correction threshold of 5.2×10^{-4}.

We further studied the association between the PRSs for myopia and POAG only in individuals from the RS with high myopia (≤–6 D, $n = 232$) and moderate myopia (–5.99 to –3.00 D, $n = 771$); see Supplementary Tables S6 and S7. In these analyses, we did not observe an association between PRSs for

Table 2. Association of PRSs for Myopia and POAG Endophenotypes

		POAG Case/Control		POAG Quantitative Traits							
		POAG		IOP		VCDR		Disc Area		Cup Area	
Score	META GWAS *P* Value Threshold	*P*	Pseudo-R^2	*P*	% Variance Explained	*P*	% Variance Explained	*P*	% Variance Explained	*P*	% Variance Explained
Reference				NA	2.07	NA	26.66	NA	19.50	NA	7.04
S1	5.0×10^{-8}	0.81	1.7×10^{-5}	0.08	0.02	0.42	*	**1.6×10^{-9}**	**0.27**	0.25	0.003
S2	5.0×10^{-7}	0.50	1.4×10^{-4}	0.10	0.02	0.44	*	**9.1×10^{-8}**	**0.21**	0.45	*
S3	5.0×10^{-6}	0.49	1.4×10^{-4}	0.03	0.03	0.29	*	**7.7×10^{-7}**	**0.18**	0.52	*
S4	5.0×10^{-5}	0.42	2.0×10^{-4}	0.01	0.05	0.63	*	**1.7×10^{-6}**	**0.17**	0.86	*
S5	5.0×10^{-4}	0.78	2.3×10^{-5}	0.02	0.04	0.42	*	**1.8×10^{-8}**	**0.24**	0.45	*
S6	0.005	0.48	1.5×10^{-4}	0.02	0.04	0.72	*	**3.2×10^{-5}**	**0.13**	0.74	*
S7	0.01	0.83	1.3×10^{-5}	0.05	0.02	0.69	*	**4.1×10^{-5}**	**0.12**	0.62	*
S8	0.05	0.70	4.4×10^{-5}	0.29	0.00	0.64	*	**2.4×10^{-4}**	**0.10**	0.68	*
S9	0.1	0.56	1.0×10^{-4}	0.25	0.00	0.73	*	**2.2×10^{-3}**	0.06	0.96	*
S10	0.5	0.52	1.3×10^{-4}	0.16	0.01	0.78	*	**2.9×10^{-3}**	0.06	0.82	*
S11	0.8	0.52	1.3×10^{-4}	0.17	0.01	0.66	*	**4.4×10^{-3}**	0.06	0.75	*
S12	1	0.51	1.3×10^{-4}	0.17	0.01	0.67	*	**4.2×10^{-3}**	0.06	0.77	*

P, *P* value of the association of the PRS for myopia with POAG and the studied POAG endophenotype, pseudo-R^2 %, and % variance explained; percentage of the variance of POAG or the studied POAG quantitative trait explained by the PRS for myopia. Reference model does not include the PRS. Boldface font: PRSs showing a significant association at a Bonferroni-corrected *P* value of $P < 5.2 \times 10^{-4}$. NA, not applicable.

* PRS in which the tested model does not improve the variance explained compared to the reference model.

Table 3. Association of PRSs for Myopia and RNFL Measured by OCT

		All Participants ($n = 2215$)		Excluding People With GVFL ($n = 2136$)	
Score	GWAS *P* Threshold	*P*	% Variance Explained	*P*	% Variance Explained
Reference		NA		NA	
S1	5.0×10^{-8}	6.31×10^{-2}	0.0662	7.19×10^{-2}	0.063
S2	5.0×10^{-7}	9.60×10^{-2}	0.0478	9.35×10^{-2}	0.051
S3	5.0×10^{-6}	1.77×10^{-2}	0.1249	1.84×10^{-2}	0.128
S4	5.0×10^{-5}	2.31×10^{-2}	0.1123	2.54×10^{-2}	0.113
S5	5.0×10^{-4}	4.56×10^{-3}	0.1899	7.82×10^{-3}	0.171
S6	0.005	4.81×10^{-3}	0.1873	7.75×10^{-3}	0.172
S7	0.01	8.88×10^{-3}	0.1576	1.05×10^{-2}	0.157
S8	0.05	6.83×10^{-3}	0.1703	1.14×10^{-2}	0.152
S9	0.1	5.44×10^{-3}	0.1813	8.70×10^{-3}	0.166
S10	0.5	1.27×10^{-2}	0.1407	1.17×10^{-2}	0.151
S11	0.8	1.21×10^{-2}	0.1427	1.16×10^{-2}	0.151
S12	1	1.22×10^{-2}	0.1422	1.17×10^{-2}	0.151

P, *P* value of the association of the PRS for myopia with RNFL. Reference model does not include the PRS.

myopia and disc area (as previously observed), but we found a suggestive association with IOP in the high myopia group (average R^2 of 0.72%, lowest *P* value = 0.01).

LD Score Regression Results

The results of our bidirectional linkage disequilibrium score regression (LDSC) analyses between POAG and its endophenotypes are shown in Table 4. Consistent with our PRS findings, we did not find evidence for a genetic correlation (RhoG) between refractive error (myopia) and most POAG endophenotypes, except for disc area (RhoG = –0.12, SE = 0.04. *P* value = 1.8×10^{-3}). We did estimate the genetic correlation between refractive error and POAG (RhoG = 0.2, SE = 0.72, *P* value = 0.78) although the standard error is large, which does not allow far-stretching inferences.

Discussion

In this study, we evaluated whether the reported epidemiologic association between myopia and POAG can be explained by a shared common polygenic structure. We used two large cohorts (a population-based study, the RS, and a case/control POAG cohort, ANZRAG), and publicly available GWAS summary statistics. Using both the classical PRS approach and the LD-score regression method, we found that genetic predisposition of myopia in the general population shows no strong association with POAG susceptibility. However, we found a robust genetic overlap between myopia and both axial length and optic nerve disc area, which supports our methodology, given that axial length is a major optical component and determinant of refractive error, and that the disc area increases proportionately with refractive error[29–31] and are therefore directly related.

There is vast epidemiologic evidence from case–control or cross-sectional studies that supports the comorbidity between myopia and POAG.[11,32–35] For example, it has been reported that 6% to 29% of POAG patients have myopia,[32] and population-based studies have shown that the odds of developing POAG are higher with increasing severity of myopia.[11,32] However, the evidence from randomized controlled trials, other population-based studies, and incidence studies is conflicting. The Ocular Hypertension Treatment Study did not find an association between myopia and POAG,[6] nor did an incidence study in Korea[36] or a population-based study in which myopia was associated only with probable but not with definite POAG.[12] However, several other incidence studies support the association between myopia and POAG.[37,38] Furthermore, it is important to note that the clinical differentiation between early-stage glaucoma and myopic changes "that look like glaucoma" is challenging. As the discs of myopic eyes might appear with large-diameter cups and nerve fiber layer defects, these findings can lead to misclassification of glaucoma in myopic eyes.[39] It has been also argued that if myopia was a risk factor for POAG, myopia should also modulate visual field loss, and therefore myopia should be associated with POAG severity, which has not been found in other studies.[40,41] Our study assessing the genetic overlap between the two conditions, in European-descent

Table 4. Results of the Genetic Correlation Between Myopia, POAG, and POAG Endophenotypes Using the LDSC Method

Trait 1	Trait 2	RhoG	SE of RhoG	*P* Value
Myopia and POAG				
Myopia META GWAS	POAG	0.2	0.72	0.78
Myopia and POAG endophenotypes				
IGGC IOP	Myopia META GWAS	−0.04	0.05	0.44
IGGC VCDR	Myopia META GWAS	−0.05	0.04	0.17
IGGC cup area	Myopia META GWAS	−0.01	0.04	0.78
IGGC disc area	Myopia META GWAS	**−0.12**	**0.04**	**1.80×10^{-3}**

Boldface font: genetic correlation showing a significant association at a Bonferroni-corrected *P* value of $P < 0.01$. IGGC, International Glaucoma Genetics Consortium.

populations, supports the results from studies in which no relationship between myopia and POAG was found.

The lack of association between myopia and VCDR (reported in this study and tested using two different approaches) has also been described by Qiu et al.,[42] in a cross-sectional study that included a representative sample from the US population. The authors found that the adjusted odds of VCDR $>$ or $= 0.7$ were not significantly increased in subjects with mild, moderate, or severe myopia.[42] However, in the same study, the authors observed an association between visual field defects and myopia.

Although we did not find an association between myopia and POAG, we did observe a nominal association between PRSs for myopia and IOP in the high myopia subgroup, and a nominal association between PRSs for myopia and RNFL. The association with IOP might be in line with previous studies, in which it has been reported that myopic eyes have a slightly higher IOP and a thinner central corneal thickness than emmetropic eyes. It has been suggested that myopia could mediate the risk of POAG through weaker scleral support.[39] Interestingly, a study examining the joint effect of IOP and myopia on the risk of POAG found that individuals with high IOP and moderate-to-high myopia had approximately 4.5-fold increased risk of POAG compared with individuals without myopia and with relatively lower IOP.[43] Regarding the nominal association with RNFL, various studies have investigated the association between various optic nerve head (ONH) parameters measured by OCT and refractive error[40,41,44] and have consistently reported a significant association between RNFL and refractive error. However, it has also been described that OCT machines do not take into account individual retinal anatomy variation, which may lead to diagnostic biases toward optic neuropathies, particularly in patients with refractive errors.[41] Furthermore, these studies[40,41] have shown that the association between RNFL and refractive error is independent of glaucoma severity. Hence, the nominal association observed between the PRSs for myopia and RNFL, rather than a truly biological association, represents the bias observed in enlarged eyes measured by OCT. In line with this notion, when we adjusted our model for axial length, the PRSs for myopia were not associated with RNFL (average $R^2 = 9.4 \times 10^{-5}$, P value $=$ 0.41, Supplementary Table S8).

Our study has several notable strengths. Firstly, our POAG phenotypes were obtained through clinical diagnosis and hence are free from self-reporting biases. Secondly, given the advance definition of POAG in ANZRAG, POAG misclassification due to high myopia is unlikely. Thirdly, our myopia PRSs capture almost 8% of the heritability on myopia (h^2 0.71),[45] showing that these PRSs are good proxies for genetic predisposition on myopia, and we found a genetic overlap between myopia and both axial length and disc area, which also validates our methodology. Finally, we used two different methods (i.e., PRS and LDSC) to evaluate the genetic overlap between these two disorders. LDSC allows meaningful interpretation of the genetic correlations without worrying about biases arising from cryptic relatedness and population stratification that might be present in PRS studies.

There are also limitations that ought to be considered when interpreting these findings. Since both ANZRAG and RS, as well as the CREAM meta-analysis, consist mainly of individuals of European ancestry, it is unclear whether our findings are generalizable to other populations. Both the PRS approach and LD-score regression evaluate shared genetic architecture from common variants; this, in turn, does not invalidate the presence of very rare variants that may exert large effects on both myopia and POAG. Hence, our inference is limited to the general population, which might not necessarily be compatible with findings from family-based eye disorders studies of rare variants. Further, the current knowledge on the genetic etiology of both disorders is limited, which also restricts our conclusions. Due to sample size concerns, we did not perform causal inference analyses such as Mendelian randomization (MR) to evaluate the direction of causality between myopia, POAG, and its endophenotypes. However, the lack of evidence for a shared genetic architecture eludes two possibilities: (1) our statistical power might be insufficient for MR and/or (2) the underlying causal relationship between myopia and POAG (and its endophenotypes) is likely to be null. In short, larger sample sizes are warranted to make robust claims about causality. In conclusion, we did not find evidence to support a genetic association between myopia and POAG. Taken together, our findings suggest that the shared genetic architecture between myopia and POAG in the general and European-descent population is likely to be limited.

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