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Self-reported myopia and age-related cataract: a two-sample Mendelian randomization study

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Our study aims to investigate whether there is evidence for a causal relationship between self-reported myopia and age-related cataract (ARC). A two-sample Mendelian randomization study was performed to identify the causal associations of self-reported myopia with ARC. We used summary-level genetic association data from the MR-Base (Mendelian Randomization-Base) platform on self-reported myopia and ARC. 26 single-nucleotide polymorphisms (SNPs) associated with self-reported myopia were used as instrumental variables. The inverse-variance weighted (IVW) method was applied to perform the primary analysis, and the weighted median method, MR-Egger regression, and Maximum likelihood methods were selected as supplementary analysis. To ensure the reliability of the results, we also performed the sensitivity analysis and MR-PRESSO analysis to assess the heterogeneity and horizontal pleiotropy. Our results provided evidence for a causal effect of self-reported myopia on ARC risk (IVW: OR 10.657, 95% CI (3.175–35.776), $P < 0.001$). The results of the weighted median method, MR-Egger regression and Maximum likelihood methods were consistent with the result of the IVW method. No evidence of heterogeneity and horizontal pleiotropy was found by the sensitivity analysis and MR-PRESSO analysis. This study demonstrated that self-reported myopia increases the risk of ARC and provided evidence to support public health interventions to prevent the onset and progress of myopia and develop new therapeutic strategies for myopia. Further large-scale prospective studies are required to validate our findings.

Keywords Myopia, Age-related cataract, Mendelian randomization, Instrumental variables, Single nucleotide polymorphisms

Age-related cataract (ARC), also known as senile cataract, is the most common type of cataract and mainly occurs in middle-aged to elderly adults above 50 years old. ARC is characterized by the opacification of the normally transparent lens with increasing age. The World Health Organization (WHO) estimated that there are 180 million visually disabled people worldwide, and cataract accounts for 46% of all cases[1,2]. ARC has become a significant global public health problem.

The etiology of ARC is unclear. The occurrence of ARC is associated with multiple complex factors, such as age, sex, race, genetic and environmental factors[1]. Meanwhile, increasing groups have focused on the relationship between myopia and ARC.

Myopia, also called short-sightedness, is considered one of the leading causes of visual impairment and vision loss in the world[3–5]. The prevalence of myopia is 10–30% in the adult population in many countries and 80–90% in young adults in some parts of East and Southeast Asia[6]. Previous studies indicated that the modern lifestyle, including the time spent on educational and outdoor or near-work activities, is the critical environmental factor contributing to myopia's development[6,7]. Genetic susceptibility is also a well-recognized factor in the onset of myopia[8]. If the progression of myopia is not promptly controlled, it may lead to a series of ocular complications, such as cataract, glaucoma, retinal detachment, optic disc changes, and maculopathy[9].

However, the relationship between myopia and ARC remains controversial in observational studies. Some studies have demonstrated that myopia is associated with an increased risk of ARC[10,11]. Individuals with myopia, especially high myopia, are more susceptible to ARC[10,12,13]. Studies suggest that myopia is not associated with the development of ARC[14]. In addition, it also remains unclear whether these associations are causal due to most of the evidence from observational studies, which are usually subject to selection biases, residual confounding, and reverse causality.

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Genetic studies have identified that gene mutations are associated with the occurrence of ARC and myopia. For example, a multiethnic genome-wide association study (GWAS) meta-analysis has identified 55 genetic loci associated with cataract[15]. CRYAA (αA-crystallin) plays a critical role in maintaining the lens transparency and the single-nucleotide polymorphisms (SNPs) rs7278468 in the CRYAA gene is associated with ARC[16]. A meta-analysis of GWAS also identified that a large number of SNPs were associated with myopia[8]. The mutation (c.228T > A, p.Tyr76*) in the ARR3 gene also contributed to the development of myopia[17]. The GWAS facilitated the development of the Mendelian randomization (MR) study[18].

Mendelian randomization approach can reduce the biases from residual confounding and reverse causality based on the independent assortment of alleles transmitted from parents to offspring during gamete formation[19]. MR, which can infer causal relationships between two complex heritable traits, has developed into a popular approach in epidemiological studies[20,21]. However, to the best of our knowledge, no MR study has investigated the associations between myopia and ARC.

The purpose of this study was to explore the potential causal effect between myopia and ARC risk using two-sample MR method.

Methods

The study design of two-sample Mendelian randomization

The two-sample Mendelian randomization was performed and reported in adherence to the guidelines for Strengthening the reporting of observational studies in epidemiology using mendelian randomization (STROBE-MR) (Supplementary table 1)[22,23]. MR analysis is a statistical method using genetic variants as instrumental variables to estimate the causal effect of exposures on outcomes[24,25]. MR analysis consists of two main steps: verifying the three core assumptions and assessing the causal relationship between the exposure and the outcome. We used the two-sample MR analysis to assess the association between myopia and ARC in the study. Self-reported myopia was used as the exposure, and ARC was used as the outcome. In the two-sample MR study, the genetic variants as instrumental variables should satisfy three assumptions: (I) the genetic variants selected as instrumental variables should be associated with myopia; (II) the used genetic variants as instrumental variables should not be associated with any known confounding factors; (III) the used genetic variants as instrumental variables should influence the risk of cataract only via myopia[26]. The MR study design was depicted in Fig. 1.

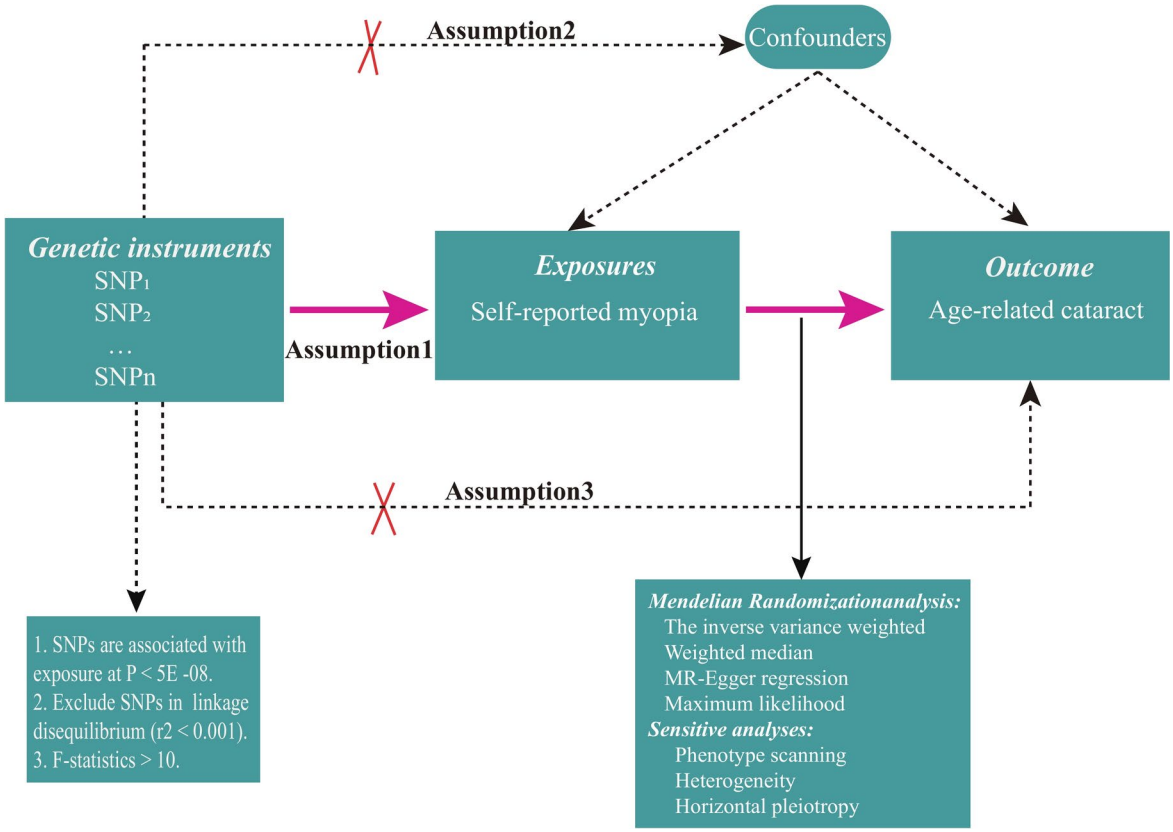

Fig. 1. The overall study design. The three core assumptions: (Assumption I) the genetic variants selected as instrumental variables should be associated with myopia; (Assumption II) the used genetic variants as instrumental variables should not be associated with any known confounding factors; (Assumption III) the used genetic variants as instrumental variables should influence the risk of cataract only via myopia.

Data for exposure and outcome

The GWAS summary data for Self-reported myopia was obtained from the MRC Integrative Epidemiology Unit (IEU) genome-wide association study (GWAS) database. The MRC IEU GWAS database was developed by the University of Bristol, which comprises 126 billion single nucleotide polymorphism-trait associations from 14,582 complete GWAS datasets[27]. Self-reported myopia is defined based on the reason for glasses/contact lenses: for short-sightedness, i.e. only or mainly for distance viewing such as driving, cinema, etc. (called 'myopia'). The genome-wide association study over 460,536 individuals of European descent, including 37,362 cases and 423,174 controls with 9,851,867 SNPs. The myopia GWAS data can be obtained from https://gwas.mrcieu.ac.uk/datasets/ukb-b-6353/.

Cataract is defined as partial or complete opacity of the crystalline lens of one or both eyes that decreases visual acuity and eventually results in blindness. The ARC cases were defined by H25-H28 in the International Classification of Disease-10 (ICD-10). Detailed information can be obtained from https://risteys.finngen.fi/endpoints/H7_LENS. The ARC GWAS recruited 216,362 individuals, including 26,758 cases and 189,604 controls. The ARC GWAS data can be obtained from https://gwas.mrcieu.ac.uk/datasets/finn-b-H7_CATARACTSENILE/. The ARC GWAS was also used in other MR study[28].

Genetic instrument selection

SNPs associated with self-reported myopia were selected as genetic instruments. During human gametogenesis, the alleles of a specific SNP are randomly distributed to egg or sperm cells. These genetic instruments are inherently immutable, providing lifelong exposure while minimizing concerns about reverse causation and reducing the influence of confounding factors[26]. Genetic instruments for self-reported myopia were selected with a genome-wide significance threshold P value $< 5 \times 10^{-8}$. We also performed the Linkage disequilibrium (LD) analysis to obtain the independent SNPs (r2 < 0.001 and clump window = 10,000 kb). Besides, palindromic SNPs with intermediate effect allele frequency were excluded from subsequent analysis. PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/) was used to assess whether the instrumental variables were associated with confounding or risk factors for disease. Age, the axial length, and liquefaction of vitreous were considered as confounding factors.

Furthermore, F statistics and variance explained (R2) were used to evaluate the strength of genetic instruments. Genetic instruments with the F statistic of less than 10 were considered weak instruments and were excluded[29].

Statistical analysis

The inverse variance weighted (IVW), weighted median, MR-Egger regression, and Maximum likelihood methids were used as Mendelian randomization models to assess the association between myopia and ARC. The inverse variance weighted (IVW) method, which could provide the most precise estimation, was applied as the primary analysis approach to evaluate the causal associations between myopia and ARC[30]. However, the IVW method is sensitive to invalid instrumental variables and pleiotropy[31]. The weighted median, MR-Egger regression, Maximum likelihood, and MR-PRESSO methods were used as supplementary analyses to increase the robustness of causal findings. When over half of the instrumental variables are valid, the median-weighted method provides a consistent estimate of the causal association between exposure and outcome[31]. The MR-Egger regression is used to detect and correct for horizontal pleiotropy, but the statistical power is low[32].

To detect underlying heterogeneity and pleiotropy in MR studies. We used Cochran's Q-statistic to test the heterogeneity of the instrument variable. The intercept from the MR-Egger regression provided a test for horizontal pleiotropy, with $P < 0.05$ suggesting the presence of horizontal pleiotropy[33]. The Leave-one-out sensitivity analysis is performed by removing one SNP at a time to evaluate the results' stability. The results are shown by drawing the forest map with a stable result intuitively judged. Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) method were used to detect and remove the possible outliers, thereby correcting for horizontal pleiotropy[34].

A total of 33 SNPs associated with myopia were selected as genetic instruments to evaluate the effect of self-reported myopia on the risk of ARC. The SNP rs36105343 was removed due to the lack of correspondence SNP in the ARC GWAS dataset. Besides, four SNPs (rs1014560, rs9557356, rs977008, rs9911460) were removed for being palindromic with intermediate allele frequency, leaving 26 potential independent instrumental variables for myopia (Table 1).

All analyses were performed using the TwoSampleMR version 0.5.6[27] and MR-PRESSO version 1.0[34] packages in R Software 4.1.2.

Results

Genetic predisposition to self-reported myopia was associated with an increased risk of ARC.

The results showed that per one standard deviation increase in self-reported myopia is associated with a higher risk of ARC (IVW: odds ratio (OR): 10.657, 95% CI (3.175–35.776), $P < 0.001$; MR Egger: OR 133.47, 95% CI (3.900–4567.058), $P = 0.012$; Weighted median: OR 8.369, 95% CI (1.642–42.643), $P = 0.011$; Maximum likelihood: OR 11.194, 95% CI (3.781–33.137), $P < 0.001$) (Table 2). The effect causal of self-reported myopia on ARC was shown in scatter plots (Fig. 2A). We also applied the Wald ratio method to estimate the causal effect of a single SNP associated with self-reported myopia on ARC. The result was shown in the forest plot (Fig. 2B).

To assess the stability of MR analysis results between self-reported myopia and ARC, we performed the sensitivity analysis using different methods. Firstly, the IVW analysis was used to test the result of heterogeneity. There was no evidence of heterogeneity (Q = 32.315, $P = 0.149$). Besides, The MR-Egger regression was used to investigate whether those genetic instruments exit potentially horizontal pleiotropy. No horizontal pleiotropy was observed in the current study (Intercept = −0.013, $P = 0.150$). Meanwhile, no outlier SNPs were identified in the MR-PRESSO. We also carried out a leave-one-out sensitivity analysis by excluding one SNP at a time to

					Myopia			Age-related cataract		
	SNPs	EA	OA	EAF	Beta	Se	*P*	Beta	Se	*P*
1	rs12193446	G	A	0.0953	−0.0123	0.0010	1.90E−37	−0.0649	0.0186	0.0005
2	rs634990	C	T	0.4891	0.0059	0.0006	1.50E−25	0.0086	0.0120	0.4732
3	rs11602008	T	A	0.1707	0.0072	0.0008	1.10E−21	−0.0001	0.0197	0.9964
4	rs2226137	G	A	0.5548	0.0054	0.0006	5.70E−21	0.0120	0.0118	0.3118
5	rs1550094	A	G	0.6952	−0.0058	0.0006	6.00E−21	−0.0259	0.0134	0.0541
6	rs10500355	A	T	0.3667	0.0055	0.0006	2.80E−20	0.0417	0.0129	0.0012
7	rs72621438	G	C	0.3510	−0.0054	0.0006	1.30E−19	−0.0350	0.0129	0.0065
8	rs12947075	T	C	0.3079	−0.0049	0.0006	2.60E−15	0.0158	0.0122	0.1967
9	rs3138142	T	C	0.2404	−0.0052	0.0007	4.80E−15	−0.0243	0.0157	0.1211
10	rs16890054	C	A	0.1897	−0.0053	0.0007	2.80E−13	−0.0012	0.0141	0.9306
11	rs10917958	T	C	0.2326	0.0045	0.0007	1.30E−11	−0.0081	0.0142	0.5710
12	rs2217839	C	T	0.5351	−0.0038	0.0006	2.90E−11	0.0028	0.0124	0.8198
13	rs1187428	C	A	0.6977	−0.0040	0.0006	1.00E−10	−0.0349	0.0132	0.0080
14	rs4515615	T	C	0.2099	0.0045	0.0007	1.10E−10	0.0004	0.0147	0.9782
15	rs1474256	T	C	0.4187	0.0037	0.0006	1.90E−10	−0.0004	0.0117	0.9699
16	rs12455102	C	A	0.1697	−0.0045	0.0008	4.60E−09	0.0060	0.0162	0.7101
17	rs2633644	T	G	0.5884	−0.0034	0.0006	5.40E−09	−0.0075	0.0116	0.5199
18	rs4792454	C	A	0.4322	0.0034	0.0006	6.70E−09	0.0109	0.0118	0.3560
19	rs4244948	T	C	0.3591	0.0034	0.0006	9.20E−09	0.0072	0.0117	0.5407
20	rs41293080	G	A	0.2004	0.0041	0.0007	1.00E−08	−0.0033	0.0153	0.8288
21	rs13399789	T	G	0.0230	−0.0109	0.0019	1.10E−08	−0.0081	0.0264	0.7596
22	rs79296018	T	C	0.0771	−0.0060	0.0011	1.50E−08	−0.0051	0.0233	0.8262
23	rs4699266	A	G	0.3436	−0.0035	0.0006	1.60E−08	−0.0078	0.0126	0.5339
24	rs2595704	G	A	0.4678	0.0032	0.0006	2.10E−08	−0.0114	0.0117	0.3279
25	rs414272	A	T	0.3276	−0.0035	0.0006	2.60E−08	−0.0068	0.0125	0.5869
26	rs2374576	T	C	0.5084	0.0032	0.0006	2.80E−08	0.0115	0.0118	0.3307

Table 1. Genetic Variants of myopia associated with age-related cataract risk. SNPs, single-nucleotide polymorphisms; EA, Effect allele; OA, other allele; EAF, effect allele frequency; Se, Standard error; *P*, *P* value.

Exposure	Outcome	Method	SNPs	Beta	Se	*P*	OR (95% CI)
Myopia	ARC	MR Egger	26	4.894	1.802	0.012	133.472 (3.901–4567.058)
		Weighted median	26	2.125	0.877	0.016	8.369 (1.499–46.717)
		Inverse variance weighted	26	2.366	0.618	< 0.001	10.657 (3.175–35.776)
		Maximum likelihood	26	2.415	0.554	< 0.001	11.194 (3.781–33.137)

Table 2. Associations of myopia and ARC in MR analysis. ARC, age-related cataract; MR, Mendelian Randomization; SNPs, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; Se, Standard error; *P*, *P* value.

assess the influence of a single SNP on the pooled results (Fig. 2C). The funnel plot is shown in (Fig. 1D). The leave-one-out sensitivity analysis result further confirmed our results' stability. The proportion of phenotypic variance explained by 26 SNPs in myopia was 3.892%. The F-statistic ranged from 30.838 to 163.580 across each SNP, and the average value was 56.031, indicating adequate strength of the genetic variants for MR analysis.

Discussion

In the current study, we performed the two-sample MR analysis to investigate the associations between self-reported myopia and ARC. Our study demonstrated that self-reported myopia increases the risk of ARC. The result was robust in sensitivity analyses that address the potential confounding effect of horizontal pleiotropy and heterogeneity in the instrumental variables.

Our study provided further evidence supporting a potential causal association between self-reported myopia on ARC risk. The result was consistent with the majority of previously published studies. A population-based cohort study of older adults found that increasing age, female gender, and myopia are the risk factors for cataract[10]. According to the location of the opacity, ARC can be divided into three major subtypes: age-related cortical cataract (ARCC), age-related nuclear cataract (ARNC), and age-related posterior subcapsular cataract (ARPSC)[35]. In the Blue Mountains Eye Study, myopia was linked to the onset of APPSC, even after

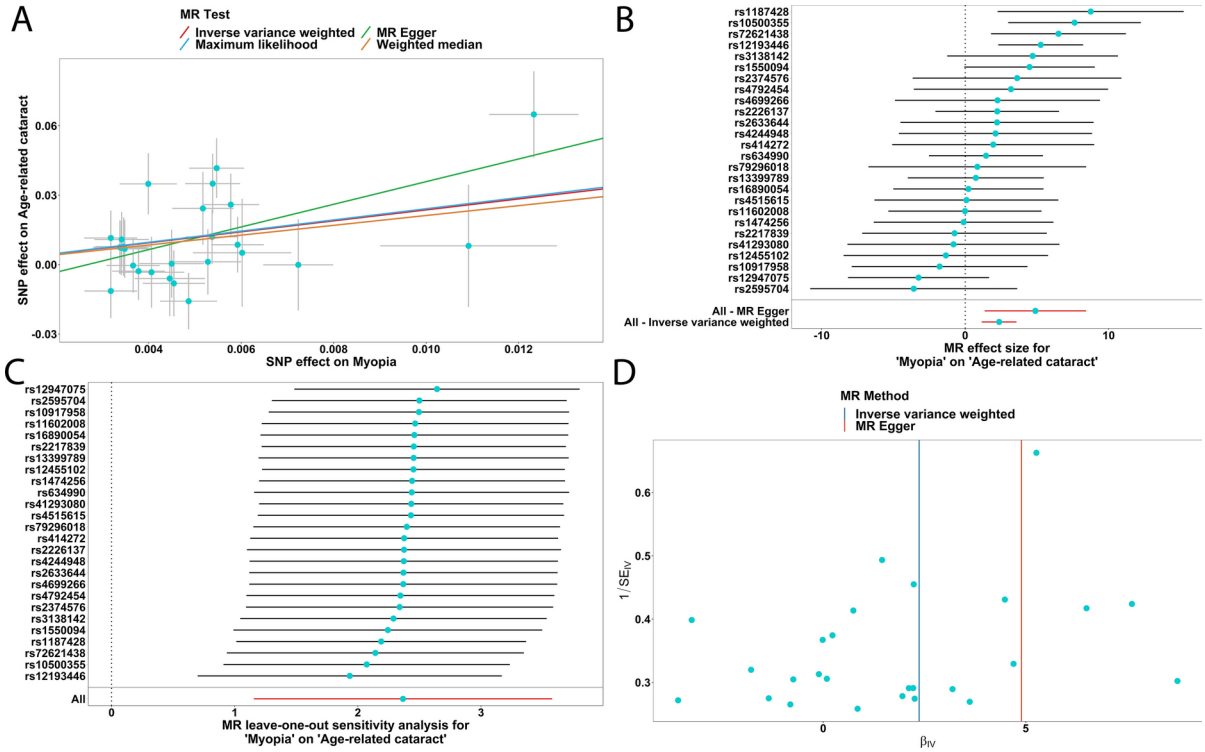

Fig. 2. Assessment of causal effects of myopia on age-related cataract. (**A**) Scatter plot showing the correlation of genetic associations of myopia with genetic associations of age-related cataract. (**B**) Forest plot of the causal effects of single nucleotide polymorphisms (SNPs) associated with myopia on age-related cataract. (**C**) Leave-one-out sensitivity analysis. (**D**) Funnel plot.

controlling for the severity of nuclear sclerosis. This study also found that people with myopia before 20 years contribute significantly to the growing risk of ARPSC[36]. Several extensive population-based cross-sectional studies also showed that myopia is significantly associated with the occurrence of ARNC[37–39]. A cohort study of Singaporeans also identified the associations between myopia and ARNC and ARPSC[40]. Besides, high myopia carries a much greater risk of ARC, which was associated with all subtypes of ARC[36]. Compared with patients with normal cataract, patients with myopia had a higher rate of postoperative complications, such as retinal detachment, posterior capsular rupture, progressed myopia traction maculopathy, capsular contraction syndrome, intraocular lens dislocation, and transient intraocular pressure elevation[41,42].

However, the association between myopia and ARC remains controversial. Chen-Wei Pan et al. investigated the associations of myopia with major age-related eye diseases, and they found that myopia is not associated with ARCC[43]. Besides, T Y Wong et al.'s study reported that myopia is not correlated with ARCC and ARPSC. They also identified that myopia is not associated with 5-year incident ARCC, ANCC, and ARPSC but with incident cataract surgery[14].

In our study, we performed a two-sample MR study with a large sample size to investigate the association between self-reported myopia and ARC. Compared with observational studies, the MR study used genetic variants as instrumental variables, reducing the bias from reverse causation and unmeasured confounding. The result of our study was robust and provided further evidence regarding the association between self-reported myopia and ARC risk.

Outlook

Myopia and ARC have already become major public health issues in most regions of the world. In terms of myopia, a recent epidemiological study has suggested that the global prevalence of myopia is almost 2 billion individuals, which accounts for 28.3% of the global population. Its global prevalence is predicted to increase to 4.76 billion individuals by 2050, which accounts for 49.8% of the global population[44]. With the increasing prevalence of myopia, it will inevitably result in increasing rates of complications, including ARC. Preventing the onset and progress of myopia and developing new therapeutic strategies for myopia are critical. It is also recommended that government and education sectors take effective and targeted preventive measures, encourage people to spend more time outdoors, and reduce near-work or educational intensity. Besides, it is also essential for people with myopia to undergo periodic ophthalmic examinations.

Strengths and limitations

The current study has several strengths and limitations. The main strengths of our study were the MR study designs, which reduced the possibility of biases residual confounding, and reverse causality from traditional

epidemiological studies. The results provided further evidence for traditional studies on the association between myopia and ARC. Besides, restricting the study sample to individuals of European descent reduced the potential population's stratification bias. There are several limiting factors in the present study. First, our study only included European ancestry participants. Thus, the results may not be generalizable to other ethnic groups. Second, myopia could be subdivided into low myopia (< −0.5 to −3 D), moderate myopia (< −3 to −6 D), and high myopia (over −6 D)[45]. The correlation between the degree of myopia and the subtypes of ARC is not considered due to the lack of the demographic characteristics of the samples. Thirdly, the potential sample overlap may reduce the validity of the results[46]. However, our data are obtained from FinnGen (ARC) and UK Biobank (myopia), and not exist the sample overlap.

Conclusion

In conclusion, this study provides strong evidence that self-reported myopia is a causal risk factor for ARC. The results of the present study provide significant clinical significance and support for public health interventions to prevent the onset and progress of myopia and develop new therapeutic strategies for myopia. Further large-scale prospective studies are required to validate our findings.

Data availability

All data generated or analyzed during this study are included in this published article. The raw data can be obtained from the IEU Open GWAS database (https://gwas.mrcieu.ac.uk/).

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Author contributions
JW and HL designed the study. WFY collected and analyzed the data. HL did the literature search and wrote the first draft of the paper. JW supervised the study.

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Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
All participating studies of GWAS have obtained approval from relevant institutional review boards, and written informed consent was received from all subjects. Summary-level data in our study are publicly available. The Medical Ethics Committee of The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology ruled that no formal ethics approval was required for this study.

Consent for publication
All authors have given their consent for publication.

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