

# Association of Myopia and Intraocular Pressure With Retinal Detachment in European Descent Participants of the UK Biobank Cohort

## A Mendelian Randomization Study

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**IMPORTANCE** Rhegmatogenous retinal detachment is a potentially sight-threatening condition. The role of myopia or intraocular pressure (IOP) in retinal detachment remains unclear.

**OBJECTIVE** To determine if myopia or IOP is associated with retinal detachment risk using genetic data.

**DESIGN, SETTING, AND PARTICIPANTS** Observational analyses and 2-sample mendelian randomization were used to evaluate the associations between myopia, IOP, and retinal detachment risk in European descent participants from the UK Biobank (UKBB) cohort (n = 405 692). For retinal detachment, a genome-wide association study on 4257 cases and 39 181 controls in the UKBB was conducted. Genetic variants associated with mean spherical equivalent (MSE) refractive error (n = 95 827) and IOP (n = 101 939) were derived using independent participants from the retinal detachment genome-wide association study. Recruitment to the UKBB occurred between 2006 and 2010, and data analysis occurred from February 2019 to March 2020.

**MAIN OUTCOMES AND MEASURES** The odds ratio (OR) of retinal detachment caused by per-unit increases in MSE refractive error (in diopters [D]) and IOP (in mm Hg).

**RESULTS** Of the 405 692 participants in the UKBB cohort, the mean (SD) age was 56.87 (7.96) years, the mean (SD) MSE was -0.31 (2.65) D, the mean (SD) corneal-compensated IOP was 16.05 (3.49) mm Hg, and 4253 participants (1.0%) had retinal detachment. Genetic analyses of the 4257 cases and 39 181 controls identified 2 novel retinal detachment genes: *COL22A1* (lead single-nucleotide variant rs11992725;  $P = 4.8 \times 10^{-10}$ ) and *FAT3* (lead single-nucleotide variant rs10765568;  $P = 1.2 \times 10^{-15}$ ). Genetically assessed MSE refractive error was negatively associated with retinal detachment (per-unit [D] increase in MSE refractive error: OR, 0.72; 95% CI, 0.69-0.76;  $P = 3.8 \times 10^{-44}$ ). For each 6-D decrease in MSE refractive error (representing the move of refractive error from emmetropia to high myopia), retinal detachment risk increased 7.2-fold (95% CI, 5.19-9.27). For per-unit (mm Hg) genetically assessed increase in IOP, the risk of retinal detachment increased by 8% (OR, 1.08; 95% CI, 1.03-1.14;  $P = .001$ ).

**CONCLUSIONS AND RELEVANCE** This study provides genetic support for the assertion that myopia and IOP are associated with the risk of retinal detachment and that myopia prevention efforts may help prevent retinal detachment.

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**R**hegmatogenous retinal detachment (RRD) is a potentially sight-threatening condition that necessitates timely intervention. It manifests when the neurosensory retina is separated from the underlying retinal pigment epithelium due to a break or tear in the neurosensory retina.<sup>1,2</sup> The incidence of RRD is between 6.3 and 17.9 in 100 000 individuals per year and the prevalence is approximately 1%, although these vary across different racial/ethnic groups and geographical regions.<sup>3</sup> Epidemiology studies have identified myopia, advancing age, and cataract operations as important risk factors for RRD.<sup>3-5</sup> For instance, the risk of RRD was increased by 3-fold for individuals with myopia.<sup>6</sup>

Several observational studies have shown an association of myopia with retinal detachment.<sup>5-7</sup> However, association is not causation, and there are many examples where the results from observational studies conflict with those from the criterion standard for causal inference, randomized clinical trials.<sup>8,9</sup> Previous studies examining the association of myopia with retinal detachment are either case series or case-control studies with a relatively small sample size and could be confounded by other risk factors, such as sex, age, and cataract surgery.<sup>3</sup>

Mendelian randomization (MR) is a statistical method that uses an instrumental variable to investigate the potential causal relationship between risk factors and outcomes.<sup>10,11</sup> In MR analysis, genetic variants (G) that are associated with an exposure (X, such as myopia) are randomly allocated at conception. If the genetic variants also affect the risk of an outcome (Y, such as retinal detachment), this helps provide evidence to support a potential causal inference about the association between the exposure and the outcome (Figure 1).<sup>11</sup> The MR analysis relies on 3 assumptions: (1) the relevance assumption that genetic variants are associated with the exposure; (2) the independence assumption that genetic variants are not associated with confounders; and (3) the exclusion restriction that genetic variants affect the outcome only through the exposure.<sup>10,11</sup>

In this study, we used MR to investigate whether genetic data provides support for a potential causal inference for the association between myopia and retinal detachment risk. Some previous studies have shown that intraocular pressure (IOP) was elevated after retinal detachment surgery.<sup>12,13</sup> However, the association of IOP with RRD remains unclear. We also used the MR method to evaluate the association of IOP with retinal detachment. Such assessment of these risk factors could have direct public health and clinical implications for prevention of retinal detachment.

## Methods

The study was approved by the National Research Ethics Service Committee North West–Haydock, all participants provided informed written consent, and all study procedures were performed in accordance with the World Medical Association Declaration of Helsinki ethical principles for medical research. Patients were not offered any compensation or incentives to participate in the study.

### Key Points

**Question** Are myopia and intraocular pressure associated with retinal detachment?

**Findings** In this 2-sample mendelian randomization analysis including nearly 500 000 participants in the UK Biobank cohort, genetic associations between myopia and intraocular pressure with the risk of retinal detachment were found.

**Meaning** These results add weight to existing evidence suggesting that myopia prevention efforts may help prevent retinal detachment.

### Study Overview

We first conducted a series of genome-wide association studies (GWASs) for retinal detachment, refractive error, and IOP in the UK Biobank (UKBB) cohort. We then used a 2-sample MR framework to investigate the associations between refractive error, IOP, and retinal detachment. For the refractive error and IOP GWASs, we removed all retinal detachment cases, controls, and their relatives ( $\pi$ -hat >0.2; identity by descent determined based on autosomal markers) to ensure samples were independent for the 2-sample MR method.<sup>11</sup> We also performed observational analyses for the association of myopia or IOP with retinal detachment to compare with the genetically derived (MR) estimates. Recruitment to the UKBB occurred between 2006 and 2010, and data analysis occurred from February 2019 to March 2020.

### Retinal Detachment Data

We identified retinal detachment cases using the following criteria: (1) *International Classification of Diseases (ICD)* diagnosis cases using *ICD-10* diagnosis code H33 (retinal detachments and breaks) and *ICD-9* diagnosis code 361 (retinal detachments and defects) or (2) self-reported retinal detachment cases from self-reported noncancer illness (UKBB code 1281, retinal detachment; UKBB data field 20002). We excluded participants with nonwhite British ancestry based on principal components.<sup>14</sup> Finally, for our retinal detachment GWAS analysis, we included 4257 retinal detachment cases and selected 39 181 controls without any eye problems or disorders from UKBB data field 6148.

For our observational analysis, we identified retinal detachment cases using similar criteria as above and used UKBB participants without retinal detachment as controls. We then removed related samples within and between retinal detachment cases and controls ( $\pi$ -hat >0.2). Finally, we included 4253 retinal detachment cases and 401 439 controls in our observational analysis.

### Mean Spherical Equivalent Data

In UKBB, refractive error was measured by an RC-5000 device (Tomey). We excluded refractometry results that were indicated as unreliable (refractometry result error in UKBB data field 5090 and 5091). We then calculated the mean values of spherical power (UKBB data field 5084 and 5085) and cylindrical power (UKBB data field 5086 and 5087) across both left and right eyes, respectively. Mean spherical equivalent (MSE)

refractive error was calculated using the formula Spherical Power + (0.5 × Cylindrical Power). The mean MSE values (across left and right eyes) were used in our analysis. We removed individuals with a history of eye surgery or eye-related complications, including eye surgery (UKBB data field 5181), cataract surgery (UKBB data field 5324), refractive laser eye surgery (UKBB data field 5325), surgery for glaucoma or high eye pressure (UKBB data field 5326), laser treatment for glaucoma or high eye pressure (UKBB data field 5327), and corneal graft surgery (UKBB data field 5328).

For the MSE GWAS analysis, we removed retinal detachment cases, controls, and their relatives ( $\pi$ -hat >0.2) to avoid sample overlap with the retinal detachment GWAS. This resulted in 95 827 individuals of white British ancestry with MSE refractive error data in the GWAS analysis.

In our sensitivity analysis, we evaluated whether high myopia or myopia was associated with retinal detachment by dichotomizing the MSE measurement. High myopia cases were defined as MSE of  $-5$  diopters (D) or less ( $n = 5824$ ) and controls as MSE greater than  $-0.75$  D ( $n = 66\ 627$ ); myopia cases were defined as MSE of  $-0.75$  D or less ( $n = 29\ 200$ ) and controls as MSE greater than  $-0.75$  D ( $n = 66\ 627$ ).<sup>15</sup>

### IOP Data

In UKBB, the corneal-compensated IOP was available for 127 455 individuals (UKBB data field 5262 and 5254) measured by the Ocular Response Analyzer (Reichert).<sup>14</sup> A detailed description of corneal-compensated IOP phenotype data was presented previously.<sup>14</sup> In brief, we calculated the mean corneal-compensated IOP across both the left and right eyes and removed measurements more than 60 mm Hg or less than 5 mm Hg. We also excluded glaucoma cases or participants who had surgery for glaucoma or high eye pressure to prevent reverse causality.

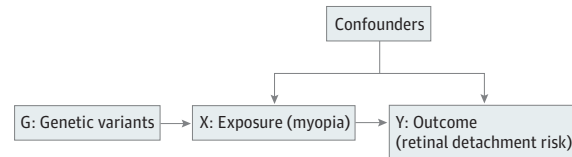
As part of the IOP GWAS analysis, we removed retinal detachment cases, controls, and their relatives ( $\pi$ -hat >0.2) to avoid sample overlap. Finally, 101 939 individuals with corneal-compensated IOP were included in GWAS analysis.

### Statistical Analysis

For the retinal detachment GWAS in UKBB, we used generalized mixed models (R package SAIGE version 0.29.6) to account for sample relatedness and unbalanced case-control ratios.<sup>16</sup> In the association analysis, we adjusted for sex, baseline age (age at recruitment), and the first 10 principal components. For the MSE and IOP GWAS analyses, linear mixed models (BOLT-LMM software version 2.3.2)<sup>17</sup> were used to account for population stratification and sample relatedness, and sex, baseline age, and the first 10 principal components were adjusted.

Linkage disequilibrium (LD) score regression method was used to estimate the genetic correlation between the traits above using only GWAS summary statistics.<sup>18</sup> To calibrate instruments for the MR analyses, we obtained genetic instruments for myopia and IOP from the above GWASs and selected independent genome-wide significant variants (significance set at 2-tailed  $P < 5 \times 10^{-8}$  and LD between single-nucleotide variants  $r^2 < 0.05$ ) for each trait of interest. The

**Figure 1. Schematic Representation of Mendelian Randomization Analysis**



Genetic variants (G) that are associated with the exposure (X, such as myopia) are used as instrumental variable. The association of genetic variants with the outcome (Y, such as retinal detachment) is only mediated through the exposure.

strength of genetic instruments was evaluated by F statistics and variance explained ( $R^2$ ).<sup>19</sup> We then conducted 2-sample MR for myopia and IOP with retinal detachment as implemented in R packages MendelianRandomization and TwoSampleMR.<sup>20,21</sup> The inverse-variance weighted (IVW) regression estimates were reported as the main analysis, and we verified the estimates using the MR weighted median and MR-Egger regression methods.<sup>22</sup> The intercept from MR-Egger regression was used to assess for horizontal pleiotropy.<sup>21</sup> We also used the MR-PRESSO method and funnel plot to evaluate bias from outliers and assess the heterogeneity of genetic instruments.<sup>21,23</sup> To assess the association of IOP with retinal detachment risk, we conducted a multivariable MR analysis, a regression-based method, to adjust for the effect of refractive error.<sup>24-26</sup> For observational analyses, we used a logistic regression model to investigate the association of MSE or IOP with retinal detachment adjusting for sex and baseline age. Analyses were performed with R software version 3.4.1 (The R Foundation).

## Results

### Observational Analysis

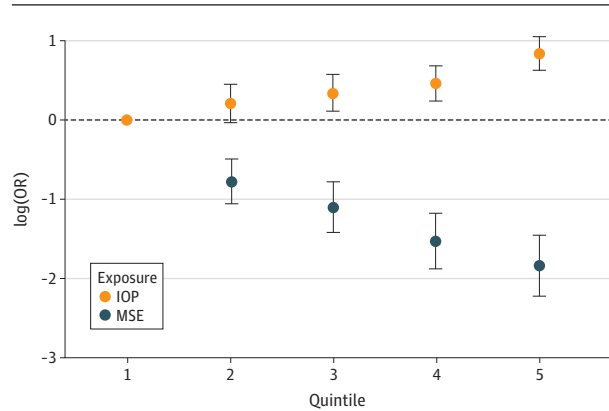
In our observational analysis of 405 692 participants in UKBB, the mean (SD) age was 56.87 (7.96) years, mean (SD) MSE was  $-0.31$  (2.65) D, mean (SD) corneal-compensated IOP was 16.05 (3.49) mm Hg, and 4253 participants (1.0%) had retinal detachment (Table 1). The risk of retinal detachment was linearly increased with decreasing MSE or increasing IOP (Figure 2). On average, for each per-unit (D) increase of MSE, the risk of retinal detachment was decreased by 28% (odds ratio [OR], 0.82; 95% CI, 0.79-0.84;  $P = 1.1 \times 10^{-47}$ ); for each per-unit (mm Hg) increase in IOP, the risk of retinal detachment was increased by 10% (OR, 1.10; 95% CI, 1.08-1.12;  $P = 6.6 \times 10^{-35}$ ). The associations were essentially unchanged after adjusting for sex and age (Table 2). There was a small but significant correlation between IOP and MSE (phenotype Pearson correlation coefficient,  $-0.076$ ;  $P = 8.3 \times 10^{-115}$ ). In observational logistic regression model, the OR of IOP for retinal detachment risk per 1-mm Hg increase was 1.05 (95% CI, 1.02-1.09;  $P = 2.5 \times 10^{-4}$ ). After adjusting for MSE, the effect size was reduced but still significant (per 1-mm Hg increase: OR, 1.03; 95% CI, 1.00-1.06;  $P = .04$ ) (Table 2).

**Table 1. Baseline Characteristics of Retinal Detachment Case and Control Sample From UK Biobank**

Variable	No. (%)		OR (95% CI) <sup>a</sup>	P value <sup>a</sup>
	Control (n = 401 439)	Case (n = 4253)		
<b>Sex</b>				
Male	184 753 (46.0)	2483 (58.4)	1 [Reference]	NA
Female	216 686 (54.0)	1770 (41.6)	0.61 (0.57-0.65)	4.3 × 10 <sup>-57</sup>
Age, mean (SD), y	56.84 (7.96)	59.78 (6.65)	1.05 (1.05-1.06)	4.1 × 10 <sup>-124</sup>
MSE, mean (SD), D	-0.31 (2.64)	-2.40 (3.75)	0.82 (0.79-0.84)	1.1 × 10 <sup>-47</sup>
No.	90 476	340	NA	NA
<b>Myopia</b>				
No	62 828 (69.4)	154 (45.3)	1 [Reference]	NA
Yes	27 648 (30.6)	186 (54.7)	2.74 (2.22-3.40)	2.3 × 10 <sup>-20</sup>
<b>High myopia</b>				
No	62 828 (91.9)	154 (63.1)	1 [Reference]	NA
Yes	5531 (8.1)	90 (36.9)	6.64 (5.11-8.62)	1.1 × 10 <sup>-45</sup>
Intraocular pressure, mean (SD), mm Hg	16.04 (3.48)	17.39 (3.90)	1.10 (1.08-1.12)	6.6 × 10 <sup>-35</sup>
No.	98 384	987	NA	NA

Abbreviations: D, diopter; IOP, intraocular pressure; MSE, mean spherical equivalent refractive error; NA, not applicable; OR, odds ratio.  
<sup>a</sup> The OR and P value were calculated from simple observational logistic regression analysis without covariates.

**Figure 2. Observational Association of Intraocular Pressure (IOP), Mean Spherical Equivalent (MSE) Refractive Error, and Retinal Detachment Risk**



The x-axis is the quintiles for exposures (IOP and MSE), and the y-axis is the natural logarithm of odds ratio (log(OR)) for retinal detachment risk. In the observational logistic regression analysis, we adjusted sex and age in logistic regression models. The figure highlights that the risk of retinal detachment is approximately linearly increased with the decreasing MSE or increasing IOP. The quintiles for MSE are -22.600 to -1.910, greater than -1.910 to -0.217, greater than -0.217 to 0.486, greater than 0.486 to 1.400, and greater than 1.400 to 14.000; the quintiles for IOP are 5.080 to 13.200, greater than 13.200 to 15.000, greater than 15.000 to 16.600, greater than 16.600 to 18.700, and greater than 18.700 to 54.400. Error bars indicate 95% CIs.

**Genetic Correlation Between Retinal Detachment, Myopia, and IOP**

We conducted a retinal detachment GWAS for 4257 cases and 39 181 controls and identified 2 novel retinal detachment genes: *COL22A1* (lead single-nucleotide variant rs11992725;  $P = 4.8 \times 10^{-10}$ ) and *FAT3* (lead single-nucleotide variant rs10765568;  $P = 1.2 \times 10^{-15}$ ) (eTable 1 and eFigures 1 and 2 in the Supplement). From LD score regression, we found very weak evidence of genomic inflation in our retinal detachment GWAS (genomic control  $\lambda$ , 1.04; LD score regression intercept, 0.98) (eFigure 1 in the Supplement). The genetic correlation between retinal detachment against MSE and IOP were

-0.45 ( $P = 1.3 \times 10^{-15}$ ) and 0.28 ( $P = 1.6 \times 10^{-6}$ ), respectively. These results indicated a high proportion of shared genetic associations between retinal detachment and myopia or IOP.

**Association of Myopia With Retinal Detachment in MR Analysis**

Myopia was measured using MSE refractive error. From the MSE GWAS, we selected 224 independent single-nucleotide variants as genetic instruments (eTable 2 in the Supplement). The F statistics and the proportion of variance-explained  $R^2$  by instruments were 54 and 0.12, respectively. In total, 10 myopia variants were associated with retinal detachment risk at a Bonferroni-corrected P value of  $P < 2.2 \times 10^{-4}$  ( $P < .05/224$ ) (eTable 3 in the Supplement). On average, MSE-decreasing alleles were associated with increased risk of retinal detachment (Figure 3) (Table 2). The MR-IVW OR of retinal detachment per 1-D increase was 0.72 (95% CI, 0.69-0.76;  $P = 3.8 \times 10^{-44}$ ) in genetically predicted MSE. The MR estimates from weighted median and MR-Egger methods were consistent with overlapping 95% CIs (eTable 4 in the Supplement). There was no evidence of directional pleiotropy inflating our estimates based on the MR-Egger intercept test (eTable 4 in the Supplement). The MR-PRESSO test also suggested there were no horizontal pleiotropic outliers to distort our result. The funnel plot showed no evidence of asymmetry (eFigure 3 in the Supplement).

In our sensitivity analysis, we also converted the continuous MSE to high myopia or myopia traits. These results indicate that higher genetic susceptibility to myopia was associated with retinal detachment (eTable 4 and eFigure 4 in the Supplement). For a binary exposure (ie, high myopia), the MR estimate represents a unit increase in the log(OR) of the exposure ( $\exp[1] = 2.72$ ), which means on average the change in the outcome for each 2.72-fold increase in the prevalence of the exposure.<sup>27</sup> This makes the interpretation of MR estimate for high myopia incomparable with the OR from observational analysis. However, if we assume there is a linear relationship between MSE and the risk of retinal detachment (Figure 2), we can derive the OR for high myopia based on MSE MR estima-

**Table 2. Mendelian Randomization (MR) and Observational Analysis Estimate of the Associations of Myopia and Intraocular Pressure (IOP) With Retinal Detachment**

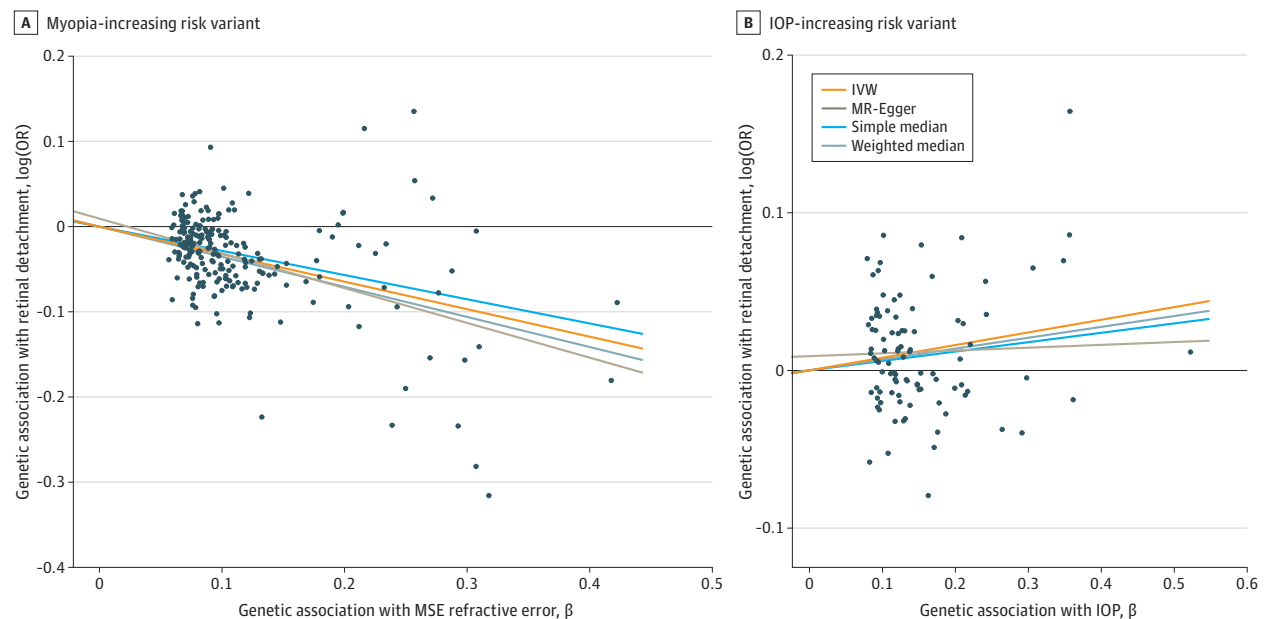
Exposure	MR method	OR (95% CI)	P value	Observational method <sup>a</sup>	OR (95% CI)	P value
MSE	IVW	0.72 (0.69-0.76)	$3.8 \times 10^{-44}$	Model 1	0.80 (0.78-0.83)	$2.5 \times 10^{-55}$
IOP	IVW	1.08 (1.03-1.14)	$1.1 \times 10^{-3}$	Model 1	1.05 (1.02-1.09)	$2.5 \times 10^{-4}$
IOP	Multivariable MR <sup>b</sup>	1.06 (1.01-1.12)	.03	Model 2	1.03 (1.00-1.06)	.04

Abbreviations: IVW, inverse-variance weighted; MSE, mean spherical equivalent refractive error; OR, odds ratio.

<sup>a</sup> In observational model 1, we adjusted for sex and baseline age in logistic regression models. In observational model 2, we adjusted for refractive error,

sex, and baseline age.

<sup>b</sup> Multivariable MR analysis, a regression-based MR method, to adjust for the effect of MSE refractive error.

**Figure 3. Association of Myopia-Increasing and Intraocular Pressure (IOP)-Increasing Risk Variants With Risk of Retinal Detachment**

A, The x-axis shows 224 genetic instruments for mean spherical equivalent (MSE) refractive error and their  $\beta$ s (effect size estimates) with refractive error. The y-axis shows the association of the same variants with retinal detachment; the y-axis unit is the effect size of single-nucleotide variants on retinal detachment in log(odds ratio [OR]). B, The x-axis shows 99 genetic instruments for IOP, and the y-axis shows the association of them with retinal detachment. The mendelian randomization (MR) inverse-weighted (IVW), MR-Egger, simple median, and weighted median regression lines are plotted.

tion ( $\exp[\log(1/0.72) \times 6] = 7.2$  [95% CI, 5.19-9.27], where 0.72 is the OR for per 1-D increase of genetically predicted MSE and 6 represents the move of refraction error from emmetropia to high myopia).

### Association of Higher IOP With Retinal Detachment in MR Analysis

From the IOP GWAS, we selected 99 single-nucleotide variants as genetic instruments (eTable 5 in the Supplement). The F statistics and the proportion of variance-explained  $R^2$  by instruments were 51 and 0.05, respectively. Intraocular pressure risk alleles were on average associated with increased risk of retinal detachment (Figure 3) (Table 2). For each unit (mm Hg) of genetically predicted increased IOP, the risk of retinal detachment increased by 8% (OR, 1.08; 95% CI, 1.03-1.14;  $P = .001$ ). There was no evidence of directional pleiotropy biasing our findings based on the MR-Egger test and MR-PRESSO global test.

In our sensitivity analysis, we removed MSE loci from IOP genetic instruments (single-nucleotide variants with  $P < .001$  in MSE GWAS), but our results were essentially unchanged (eTable 4 in the Supplement). We also conducted a multivariable MR analysis to assess the association of IOP with retinal detachment after adjusting for the effects from MSE. The association of IOP with retinal detachment did not essentially change after the adjustment of MSE (OR, 1.06; 95% CI, 1.01-1.12;  $P = .03$ ) (Table 2). The results from multivariable MR analysis were also similar to an observational logistic regression model adjusting for the effects of MSE exhibiting overlapping 95% CIs (Table 2).

## Discussion

We have conducted an observational and an MR analysis to investigate the associations between myopia and IOP with reti-



nal detachment risk. Our MR analysis provided support for a potential causal inference for the associations of myopia and IOP with retinal detachment; the risk of retinal detachment was linearly increased with a higher level of myopia or IOP. Our sensitivity analyses support our main results, providing support for a potential causal association between myopia and retinal detachment.

Myopia is a leading cause of vision impairment worldwide, and its prevalence is increasing rapidly.<sup>28</sup> Myopia is often considered benign because it could be easily corrected with contact lenses, glasses, or surgery.<sup>29</sup> Clinically, pathological myopia with pathological signs of myopic maculopathy, myopic crescent, posterior staphyloma, or myopic optic neuropathy is often observed in eyes of high myopia rather than in eyes with a mild to moderate degree of myopia.<sup>28,30</sup> Previous epidemiological studies have shown an association of myopia with retinal detachment.<sup>5-7</sup> However, these studies are either case series reports or case-control studies with a relatively small sample size. In our study, the large sample size and well-measured MSE refractive error data exhibited a linear association between the degree of myopia and the risk of retinal detachment. In traditional observational studies, the association of myopia with retinal detachment could be confounded by other risk factors, such as sex, age, eye trauma, and cataract surgery. For instance, in our UKBB observational analysis, participants with high myopia had 2.5-fold increased risk of cataract compared with participants without myopia. Since cataract operation is also a risk factor for retinal detachment, the association of high myopia with retinal detachment could be partly confounded by cataract in observational analysis. The advantage of this study is that we used the MR method to investigate the association of myopia with retinal detachment. The robustly associated genetic instruments from several myopia proxy traits yielded similar results. These results reinforce that myopia is not a benign condition that can be trivially fixed with spectacles, and even a mild to moderate degree of myopia could cause serious eye complications.

To our knowledge, there are no previous studies investigating the association of IOP with retinal detachment. However, some studies showed that IOP was elevated after retinal detachment surgery.<sup>12,13</sup> In this study, we used genetic data to evaluate the association of IOP with retinal detachment among adults of European descent. Our observational and MR results indicated higher levels of IOP were associated with retinal detachment. In our sensitivity analysis where we adjusted for MSE or removed MSE-related single-nucleotide variants, the effect size of IOP on retinal detachment risk attenuated very slightly (multivariable MR per 1-mm Hg increase: OR, 1.06; 95% CI, 1.01-1.12;  $P = .03$ ). A previous study indicated that elevated IOP may increase the stretching stress on the sclera, choroid, and retina.<sup>31</sup> However, further functional studies are warranted to investigate the underlying biological mechanism(s) between IOP and retinal detachment.

A concern in MR analysis is that a valid causal inference relies on the 3 MR assumptions. In this study, we investigated these assumptions using both biological knowledge and various statistical methods. First, we conducted GWASs for re-

fractive error and IOP with large sample size, and the genetic variants are strong genetic instruments (relevance assumption). To our knowledge, there are no alternative biological pathways that can influence the associations of genetic instruments and retinal detachment risk (biological knowledge). We also used various MR methods (MR-Egger, weighted median, MR-PRESSO, and multivariable MR methods) that yield consistent estimates in the presence of invalid instruments in our sensitivity analysis to triangulate our causal inference. Notably, we found very weak evidence of pleiotropic effects (independence assumption and exclusion restriction). These analyses indicated that our findings were unlikely to be biased by violation of MR assumptions.

### Limitations

Our results should be interpreted in light of their limitations. In our retinal detachment GWAS, we identified retinal detachment cases using both hospital health records and self-reported retinal detachment cases, and retinal detachment cases could include different subtype cases. However, a 2020 study<sup>32</sup> showed that self-reported retinal detachment cases displayed similar epidemiologic features as ICD-defined cases. When we restricted retinal detachment cases to ICD-defined cases, the MR results were essentially unchanged (eFigure 5 in the Supplement). We further only used cases identified as ICD-10 code H330 (retinal detachment with retinal break). The MR-IVW OR of retinal detachment (only including cases using ICD-10 code H330) was 0.69 (95% CI, 0.64-0.74;  $P = 5.6 \times 10^{-24}$ ) per unit (D) increase in genetically predicted MSE. For each unit (mm Hg) of genetically predicted increased IOP, the risk of RRD increased by 10% (OR, 1.10; 95% CI, 1.03-1.19;  $P = .007$ ). The MR estimates were essentially unchanged, although as expected with lower power (and consequentially, the confidence intervals were wider). Second, we only conducted myopia, IOP, and retinal detachment GWASs in participants of European ancestry; thus, the generalizability of our findings in other racial/ethnic groups still needs further investigation. Third, the presence of horizontal pleiotropy (genetic instruments affecting the outcome through another pathway rather than the exposure) may violate one of the MR assumptions.<sup>11</sup> However, in our MR sensitivity analysis, we conducted the MR-Egger intercept test and the MR-PRESSO global test and found no evidence for directional horizontal pleiotropy inflating our estimates. Given the large effect size for the association between myopia and RRD and the weak correlation between myopia and IOP, it remains possible that the effect size for the association IOP and RRD is confounded by the association of myopia with RRD. Our multivariable MR analysis suggests the IOP association was independent of the myopia association, although we cannot rule out the IOP association being driven by myopia (or another unknown confounder). A further specific limitation of our multivariable MR method is that the association between myopia and IOP was assumed to be linear; since this is difficult to assess, we cannot be certain that the associations for myopia and IOP with retinal detachment are truly independent.

## Conclusions

Our study provides evidence supportive of a potential causal association between both myopia and IOP on retinal detachment risk. Such assessment of these risk factors could have

direct public health and clinical implications for prevention of retinal detachment. Further research is required to determine whether reducing progression of myopia of an individual through interventions such as topical atropine<sup>33</sup> or time spent outdoors<sup>34</sup> will modify the risk of retinal detachment.

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**Author Contributions:** Mr Han had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Han, Craig, Hewitt, MacGregor.

**Acquisition, analysis, or interpretation of data:** Han, Ong, An, Craig, Gharahkhani, MacGregor.

**Drafting of the manuscript:** Han, Ong, MacGregor.

**Critical revision of the manuscript for important intellectual content:** All authors.

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### Invited Commentary

## Rhegmatogenous Retinal Detachment in the Age of Genomic Medicine

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**Rhegmatogenous retinal detachment (RRD)** happens when a vitreous humor-filled gap forms between the neurosensory and the retinal pigment epithelium layers. Although the condition is relatively infrequent and has surgical repair success rates greater than 80%,<sup>1</sup> the visual acuity outcomes are poor in half of cases, especially patients who present with a detached macula.<sup>2</sup> Male sex, myopia, and cataract surgery are all risk factors disproportionately overrepresented among patients with RRD. Because of the difficulty assembling sufficiently well-powered prospective studies, which is particularly intense for low-frequency disorders such as RRD, quantifying how much risk is associated with the presence of each factor and establishing the nature of their association with retinal detachment remains elusive.

This is precisely the question that Han et al<sup>3</sup> take on in an article published in this issue of *JAMA Ophthalmology*. Instead of longitudinally observing a large number of participants to link RRD incidence with specific susceptibility factors, they take advantage of large-scale genomic information on myopia and intraocular pressure (IOP) recently made available from the UK Biobank and compare them with RRD risk through a statistical technique called mendelian randomization. This approach is akin to a naturally designed clinical trial, although it is not a randomized clinical trial. Each person at birth is randomly allocated 1 allele at each of the tens of millions of sequence-variable DNA locations. Some of these single-nucleotide variants confer a specific amount of risk to any trait or disease. The mendelian randomization method in this study effectively stratified thousands of UK Biobank participants according to the spherical equivalent and myopia burden allocated at birth. Participants with a higher dose of myopia-associated single-nucleotide variant alleles mimic the intervention arm in a clinical trial, and others represent control participants. Incidents of RRD in patients exposed to various degrees of genetically associated myopia represent the clinical trial outcome. Estimates are thought not to be biased by coincident factors, such as the environment, because what distinguishes both arms from each other—the genetic risk—is regarded as immutable from birth.<sup>4</sup>

The authors<sup>3</sup> confirm observational data analyses that the spherical equivalent is negatively correlated with RRD. In addition, they find evidence that for each 1-diopter decrease in spherical equivalent, the detachment risk increases by 38%. By applying identical mendelian randomization techniques,

the authors also report (to our knowledge, for the first time) that each 1-mm Hg increase in IOP is associated with an increase in the likelihood of RRD of 6% to 8%.

This study<sup>3</sup> provides an example of why increasingly larger-scale genetic association studies are more than simple exercises frivolously incrementing the number of weak-association genes statistically annotated to a given trait. Indeed, when sufficiently powered, these population-based data analyses can be effectively used to characterize risk factors contributing to any disease in detail, even rare ones, such as RRD. This only became possible relatively recently because of advances in statistical methodology and increased availability of big genomic data, through which hundreds of DNA sequence variants associated with thousands of different traits and diseases were uncovered.

Individualized risk profiling of patients can improve monitoring and lead to better visual outcomes through early detection of retinal tears. Han et al<sup>3</sup> already provide good estimates of the lifelong RRD risk associated with refractive status in eyes with phakic intraocular lenses. Building on these strengths, the accuracy of future predictive models may further improve by incorporating information about the temporal patterns of RDD incidence and improved understanding on the outcome of more severe forms of myopia over RDD. Because incidence in eyes with phakic lenses seems to peak in the third decade of life,<sup>5</sup> the risk attributable to myopia could vary with age. It is also not entirely clear whether the outcomes of RRD observed over the mean spherical equivalent spectrum are linearly scalable and proportionally apply to high myopia, because the current study could only use DNA sequence variations associated with putatively normal spherical equivalent variation as mendelian randomization instruments.

This work<sup>3</sup> points to the IOP as a first potentially modifiable risk factor to RRD. Although caution is warranted over its relevance as an independent RRD risk factor, apart from the refractive status with which it is correlated; early evidence suggests that IOP is significantly associated with the odds of retinal detachment. In absence of effective preventive alternatives,<sup>6</sup> the potential clinical benefits of IOP-lowering treatments should not be overlooked.

In addition to answering specific questions, good scientific research is also judged by the importance of new questions it raises and the fresh perspectives it opens. Future work will now be needed to comprehensively address all relevant



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