Refractive Error Has Minimal Influence on the Risk of Age-Related Macular Degeneration: A Mendelian Randomization Study

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• PURPOSE: To test the hypothesis that refractive errors such as myopia and hyperopia cause an increased risk of age-related macular degeneration (AMD) and to quantify the degree of risk.
• DESIGN: Two-sample Mendelian randomization analysis of data from a genome-wide association study.
• PARTICIPANTS: As instrumental variables for refractive error, 126 genome-wide significant genetic variants identified by the Consortium for Refractive Error and Myopia and 23andMe Inc. were chosen. The association with refractive error for the 126 variants was obtained from a published study for a sample of 95,505 European ancestry participants from UK Biobank. Association with AMD for the 126 genetic variants was determined from a genome-wide association study (GWAS) published by the International Age-related Macular Degeneration Genomics consortium of 33,526 (16,144 cases and 17,832 controls) European ancestry participants.
• METHODS: Two-sample Mendelian randomization (MR) analysis was used to assess the causal role of refractive error on AMD risk, using the 126 genetic variants associated with refractive error as instrumental variables, under the assumption that the relationship between refractive error and AMD risk is linear. Main outcome measurement: the risk AMD was caused by a 1-diopter (D) change in refractive error.
• RESULTS: MR analysis suggested that refractive error had very limited influence on the risk of AMD. Specifically, 1 D more hyperopic refractive error was associated with an odds ratio (OR) of 1.080 (95% confidence interval [CI], 1.021-1.142; $P = 0.007$) increased risk of AMD. MR-Egger, MR pleiotropy residual sum and outlier, weighted median, and Phenoscanner-based sensitivity analyses detected minimal evidence to suggest that this result was biased by horizontal pleiotropy.
• CONCLUSIONS: Under the assumption of a linear relationship between refractive error and the risk of AMD, myopia and hyperopia only minimally influence the causal risk for AMD. Thus, inconsistently reported strong associations between refractive error and AMD are likely to be the result of noncausal factors such as stochastic variation, confounding, or selection bias. (Am J Ophthalmol 2019;206:87–93. © 2019 Elsevier Inc. All rights reserved.)

AGE-RELATED MACULAR DEGENERATION (AMD) IS among the leading causes of visual impairment worldwide, and the leading cause in economically developed countries such as the United Kingdom where it is responsible for more than 50% of registered visual impairment.[1] The socioeconomic burden due to AMD-related visual impairment is set to increase even further as the elderly population expands.[2,3] AMD is a progressive condition that affects the macular region of the retina. The early stage is characterized by increasing drusen (number, size, and confluence) and pigmentary abnormalities in which vision is usually minimally affected. Advanced disease may manifest either through gradual, progressive atrophy of the macula or rapid development of subretinal neovascularization leading to edema, hemorrhage, and eventual scar formation. Both atrophic and neovascular forms are associated with contemporaneous and often severe adverse effects on central vision. Currently, treatment is only available for the neovascular form of AMD. The most effective treatment involves regular injections of anti- vascular endothelial growth factor (VEGF) drugs into the eye.[4–6] The development of new treatments and therapies requires a better understanding of the cause and pathogenesis of AMD, so that disease mechanisms can be effectively targeted. Recognizing causal risk factors for AMD is therefore key to this work.

Although the cause of AMD is not fully understood, it is clear that the condition results from a combination of genetic and environmental factors, the identification of which has been important in informing the understanding of AMD pathogenesis.[7,8] The principle risk factor for AMD is age.[9–12] Of the additional known risk factors, genetic predisposition and smoking have been the most consistently and confidently identified, the latter having particular significance as the risk can be modified with intervention. A systematic review by Chakravarthy and

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associates[9] identified 73 potential risk factors for advanced AMD, covering environmental (eg, ultraviolet/sun exposure), demographic (eg, age, race/ethnicity), genetic (eg, complement factor H), lifestyle (eg, smoking, dietary fats, and antioxidants), general health (eg, cardiovascular disease), and ocular comorbidity (eg, refractive error) factors. Nevertheless, few of these potential risk factors for AMD have been evaluated as part of a randomized control trial (RCT) designed to test for a causal role. Although RCTs are the gold standard for demonstrating causation, they are resource intensive and are not always practical (eg, if a long-term intervention is required, an RCT may not be feasible; or if exposure to a risk factor poses a potential health risk, an RCT may be unethical).

Refractive error, particularly hyperopia, has been suspected to increase the risk of AMD since at least the late 1970s.[13] However, despite research over many decades, the evidence from cross-sectional and cohort studies has been inconsistent.[14,15] Standard cross-sectional observational studies are susceptible to confounding and therefore are unable to establish a casual association between an exposure (eg, degree of refractive error) and an outcome (eg, patient has AMD).[16,17] Mendelian randomization (MR) analyses have been proposed as a research method for drawing valid casual inferences using existing, cross-sectional datasets,[16,18] either as an alternative to RCTs in circumstances when an RCT is not practical or as a precursor before embarking on a lengthy and costly RCT.[19] MR uses genetic variants that explain variation in an exposure as instrumental variables [20] in order to quantify the effect of the exposure on the outcome, independent of confounding factors that influence the exposure-outcome relationship. The ability to attribute a causal effect in MR depends primarily on the following 3 key assumptions: (1) the genetic variants are robustly associated with the exposure; (2) the genetic variants only affect the outcome through the exposure; and (3) the genetic variants do not exert effects on confounders of the exposure-outcome relationship. The present study tested the hypothesis that refractive error has a causal impact on the risk of AMD by applying Mendelian randomization, using as instrumental variables genetic variants associated with refractive error in a recent, large-scale genome-wide association study (GWAS).

SUBJECTS AND METHODS

THE STUDY DESIGN IS A 2-SAMPLE MR USING GWAS SUMmary statistics from the Consortium for Refractive Error and Myopia (CREAM), 23andMe (Mountainview, California), UK Biobank (Stockport, Greater Manchester, United Kingdom), and the International Age-related Macular Degeneration Genomics Consortium (IAMDGC, National Center for Biotechnology Information, Bethesda, Maryland, USA). Participants provided informed consent to take part in the studies, which adhered to the principles of the Declaration of Helsinki.[21,22] The School of Optometry and Vision Sciences Research Audit Ethics Committee IRB provided a waiver confirming approval was not required as this was a retrospective analysis of data already in the public domain.

• **INSTRUMENTAL VARIABLES FOR REFRACTIVE ERROR:** Tedja and associates[21] reported the largest GWAS meta-analysis for refractive error to date. The GWAS meta-analysis included data for 160,420 participants of European ancestry from the CREAM consortium and the 23andMe personal genomics company. The CREAM consortium GWAS was performed for the spherical equivalent refractive error (SER) trait, whereas the trait analyzed in the 23andMe GWAS was age of diagnosis of myopia (AODM). Tedja and associates[21] identified 161 lead variants, where a lead variant was defined as "the variant with the lowest P value in a 100-kb window of the outermost genome-wide-significant variant of that same region." These 161 variants with a P value $<5 \times 10^{-8}$ in the CREAM and 23andMe GWAS were tested for replication in an independent sample of 95,505 participants of European ancestry 37-73 years of age from UK Biobank who had no history of eye disorders.[23] All UK Biobank participants had phenotype information for SER measured using noncycloplegic autorefraction in diopters (D). The mean $\pm$ standard deviation age of the UK Biobank GWAS sample was 57.7 $\pm$ 7.9 years old, and 53.1% were female. A total of 149 of 161 variants provided independent evidence of replication in the UK Biobank sample ($P < 0.05$) after excluding 1 tri-allelic variant.[21] From among these 149 variants, 18 (rs10003846, rs11723482, rs1207782, rs13069734, rs1550094, rs17400325, rs17837871, rs1994840, rs2276560, rs2326823, rs2573081, rs2823097, rs6903823, rs72621438, rs745480, rs7925340, rs79266634 and rs79953651) were excluded as potential instrumental variables for having a pairwise linkage disequilibrium (LD) coefficient of determination (r^2) >0.05 with another variant in the set, and an additional 2 markers (rs1983554 and rs931302) were excluded for having a Hardy-Weinberg equilibrium test of $P < 0.05$, leaving 129 independent variants. There were 24 palindromic single nucleotide polymorphisms (SNPs) (ie, SNPs with alleles A/T or C/G, among these 129 variants). To avoid the chance of incorrectly harmonizing alleles in the 2-sample MR analysis,[24] palindromic SNPs were replaced by proxies in high LD ($r^2 > 0.8$); proxies were available for 21 of the 24 palindromic SNPs, leaving a final set of 126 variants which were used as instrumental variables for refractive error in the current study (no proxy was available for rs2908972, rs74764079, or rs807037). The degree of association with refractive error for the variants was taken from the UK Biobank replication sample, rather than the larger CREAM/23andMe discovery sample, because the trait analyzed in the UK Biobank GWAS was SER for all participants.

The summary statistics for the 126 refractive error instrumental variables are shown in Supplemental Table (available at www.aaojournal.org).

• **ASSOCIATION OF INSTRUMENTAL VARIABLES WITH AGE-RELATED MD:** Fritsche and associates[22] reported a GWAS meta-analysis for AMD carried out by the IAMDGC. This meta-analysis examined a discovery sample of 33,526 individuals (16,144 cases and 17,832 controls) recruited across 26 studies. AMD cases were defined as individuals with either geographic atrophy and/or choroidal neovascularization in at least 1 eye and were ≥50 years of age at first diagnosis (advanced AMD), or as individuals with pigmentary changes in the retinal pigment epithelium or more than 5 macular drusen 63 μm or greater in diameter and ≥50 years of age at first diagnosis (intermediate AMD). Control participants were 70.7 ± 9.7 years of age and were free from advanced or intermediate AMD. The GWAS meta-analysis summary statistics reported by the IAMDGC included the effect allele, reference allele, direction of effect (ie, increased or decreased risk of AMD), and *P* values. For MR analysis, the log(odds ratio [OR]) and corresponding standard errors for this dataset were calculated as described by Burgess and Davey Smith.[25] Of the 126 genetic variants selected as instrumental variables for refractive error, summary data for all 126 were available in the AMD GWAS dataset.

• **STATISTICAL ANALYSIS:** All analyses were carried out with R software (R Foundation, Vienna, Austria).[26] Inverse variance-weighted (IVW) MR,[27] under a multiplicative random effects model, weighted median MR[28] and MR-Egger analyses[29] were carried out with MR software.[30] MR pleiotropy residual sum and outlier (MR-PRESSO) analysis was performed using MR-PRESSO software, with K = 100,000 simulations.[31] Scatter plots were generated with the "ggplot2" software. I^2 heterogeneity statistics were calculated using "metafor" software.[32] From among the 126 variants associated with refractive error selected as instrumental variables, those with known pleiotropic effects on additional traits were identified using Phenoscanner (University of Cambridge, Cambridge, United Kingdom)[33] with the settings $P < 5 \times 10^{-8}$ and inclusion of proxy variants in LD ($r^2 > 0.8$) in Europeans. The Phenoscanner (analysis identified 31 variants with known pleiotropic effects) (Supplemental Table; available at www.aaojournal.org). The variance in refractive error explained by the 126 instrumental variables was assessed as described by Ghorbani Mojarrad and associates[34] in a sample of 1,516 unrelated female adults from the United Kingdom (44.6 ± 4.4 years of age) whose refractive error was assessed by noncycloplegic autorefraction. Statistical power was assessed as described by Brion and associates[35] using the online tool: http://cnsgenomics.com/shiny/mRnd/.

RESULTS

A TOTAL OF 126 GENETIC VARIANTS ASSOCIATED WITH refractive error were chosen as instrumental variables for refractive error. The 126 genetic variants explained 4.4% of the variance in refractive error in an independent sample of UK adults, and the F-statistic from the first stage of the MR analysis was 1544.0. Both of these findings suggested there was minimal risk of weak instrument bias.[34] The study had 45% power to detect an OR of 1.10 increased risk of AMD per 1 D more hyperopic refractive error, and 80% power to detect an OR of 1.16 increased risk. Hence, the study was well powered to detect risks below OR of 0.85 or above OR of 1.15 but was not well powered to detect very small risks close to the null value.

A quantile-quantile (QQ) plot for the 126 refractive error instrumental variables designed to illustrate their association with AMD demonstrated an excess of low *P* values compared to that expected under the null hypothesis (Figure 1). In particular, 2 of the refractive error variants were very strongly associated with AMD risk: rs10760673, an intronic variant within the TGFBR1 gene (AMD risk *P* = 4.59e-09); and rs6420484, a missense variant in the *TSPAN10* gene (AMD risk *P* = 4.11e-11). Both genetic loci were already well known to be associated with AMD (Figure 1).[22]

A standard IVW MR analysis using all 126 genetic variants suggested that each 1.00- D change in refractive error in the direction of more hyperopia was associated with an approximately 8% increase in the risk of AMD (OR, 1.080; 95% CI, 1.021-1.142; *P* = 0.007) (Table 1, Figure 2).

The standard IVW MR analysis including all 126 genetic variants exhibited strong evidence of heterogeneity (Cochran Q, 326.1; *P* = 7.1e-20; I^2 = 61.6%), implying that the SNP-exposure vs. SNP-outcome relationship varied widely across variants. The most likely reason for such heterogeneity in an MR analysis is "horizontal" pleiotropy.[18] Hence, a series of sensitivity analyses were undertaken to examine the robustness of the IVW MR causal effect estimate (Tables 1-3). A weighted median-based MR analysis, which provides a valid causal effect estimate if up to one-half of the information is from invalid instrumental variables, produced a similar estimate to that obtained from the IVW MR but with weaker statistical support. Specifically, although the median-based MR estimate was consistent with the IVW MR estimate, the 95% CI included the null value (OR, 1.045; 95% CI,: 0.982-1.111; *P* = 0.164) (Table 1), commensurate with the reduced statistical power of median-based MR compared to IVW MR.[28] An MR-Egger analysis found negligible evidence of directional pleiotropy: MR-Egger intercept of 1.003 (95% CI: 0.991-1.016). Repeating the above analyses after excluding the 2 variants (rs10760673 and rs6420484) very strongly associated with AMD risk had minimal impact on the results (Table 2). In addition

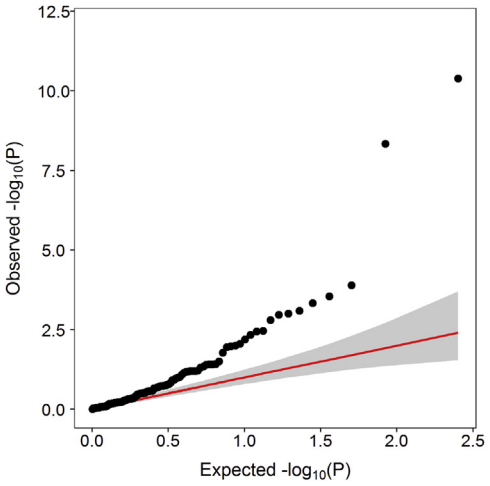

FIGURE 1. Quantile-quantile plot illustrating the observed level of association with age-related macular degeneration (AMD) risk (negative $\log_{10}$ *P* value) for 126 genetic variants used as instrumental variables for refractive error. Note the inflation of observed negative $\log_{10}$ *P* values compared to those expected under the null hypothesis of no association with AMD risk. The red line is the line of unity and the gray shaded region is the 95% confidence interval expected under the null hypothesis. Each point represents an individual genetic variant.

TABLE 1. Mendelian Randomization Cause Estimate for the Risk of AMD Per 1 Diopter More Hyperopic Refractive Error

Analysis	Cause Effect (OR per D)	95% Confidence Interval	*P* Value
Inverse variance-weighted	1.080	1.021-1.142	0.007
Weighted median	1.045	0.982-1.111	0.164
MR-Egger	1.048	0.922-1.190	0.474
Analysis	**Intercept**	**95% Confidence Interval**	***P* Value**
MR-Egger	1.003	0.991-1.016	0.609

AMD = age-related macular degeneration; D = diopter; MR = Mendelian randomization; OR = odds ratio.

to the 2 variants associated with AMD, a Phenoscanner analysis[33] identified a further 29 genetic variants with known effects on traits unrelated to refractive error. MR analysis after exclusion of these 31 variants from the original set of 126 variants produced findings comparable to those in the original analyses (Table 3). For example, the IVW MR causal effect estimate was OR of 1.069 (95% CI: 1.016-1.124; $P = 0.010$). Heterogeneity was partially reduced in this analysis compared to the original analysis with all 126 variants (Cochran Q, 161.6; $P = 1.81e\text{-}05$; $I^2 = 39.1\%$). Finally, an MR-PRESSO analysis identified 6 variants as pleiotropic outliers (Supplemental Table; available at www.aaojournal.org). After these 6 variants were removed, the MR-PRESSO causal effect estimate was OR of 1.104 (95% CI: 1.054-1.157; $P = 8.12e\text{-}05$) (Tables 2 and 3).

In summary, a wide range of MR analysis models all produced causal effect estimates close to the null, with the most highly statistically powered analysis estimating an approximate 8%-10% increased risk of AMD per 1 D more hyperopic refractive error.

DISCUSSION

A 2-SAMPLE MR ANALYSIS WAS PERFORMED TO DETERMINE whether a causal relationship exists between refractive error and the risk of AMD based on genetic data from populations with European ancestry. The results suggested that the SER does indeed have a causal relationship with AMD risk, albeit with the risk of AMD increasing by less than 10% per 1-D increase in hyperopia. This study provides genetic evidence to support a causal link between refractive error and AMD risk, which although not as definitive as that obtained from an RCT, provides greater freedom from confounder bias than the risks reported in the observational epidemiological studies conducted to date.

A meta-analysis carried out by Pan and associates [14] suggested that each 1 D of increase in hyperopia is associated with a 6%-9% increased risk of AMD based on pooled responses across 2 cohort and 5 cross-sectional studies. A further meta-analysis by Li and associates,[15] using largely overlapping study samples as did Pan and associates,[14] perhaps unsurprisingly found a similarly increased risk of 6%-10% per diopter increase in hyperopia. Both figures are consistent with the upper estimate found in the present analyses of an approximately 8%-10% increased risk of AMD per diopter of hyperopia. However, when making this comparison, it is important to note Pan and associates[14] observed that, other than age, many important confounders, such as smoking status, education level, and socioeconomic status, were not accounted for across all the meta-analyzed studies. Furthermore, neither meta-analysis[14,15] limited inclusion to individuals of European ancestry in contrast to the present MR analysis.

Various biologically plausible explanations have been proposed for the relationship between refractive error and AMD risk. Explanations previously explored include posterior vitreous detachment, the prevalence of which is greater in myopic eyes,[36] which has been suggested to reduce the likelihood of neovascularization[14,37] (with the posterior vitreous detachment hypothesized as removing a barrier to diffusion of VEGF away from the macular). Also, the VEGF concentrations in the retina have been reported to be lower in myopic than in hyperopic eyes, leading Jonas and associates[38] to propose that this reduced VEGF concentration may influence the risk of AMD.

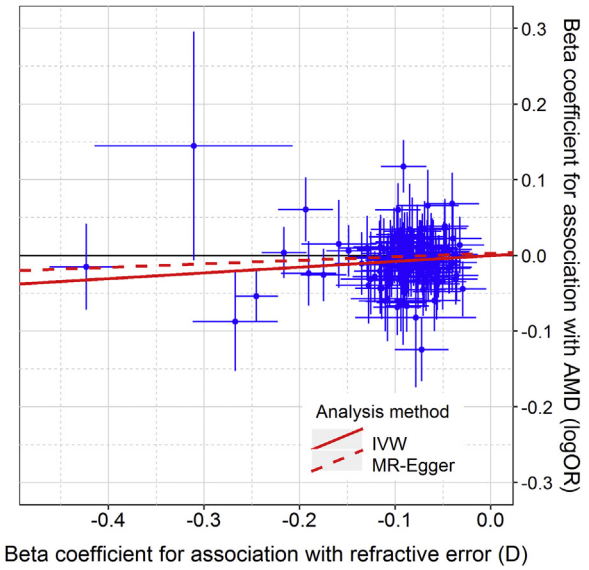

FIGURE 2. Graphic representation of 2-sample Mendelian randomization (MR) meta-analysis results. Each point represents an individual genetic variant (instrumental variable) with error bars indicating the standard error. The association between each genetic variant and refractive error (in units of diopters per copy of the risk allele) is plotted on the x-axis, and the association between AMD risk (log odds ratio) is plotted on the y-axis. The solid red line shows the fit from an inverse variance weighted (IVW) MR meta-analysis model, and the dashed red line shows the fit for an MR-Egger model.

TABLE 2. Sensitivity Analysis Results for Mendelian Randomization Analyses after Excluding 2 Variants (rs10760673 and rs6420484) Strongly Associated with AMD Risk

Analysis	Cause Effect (OR per D)	95% Confidence Interval	*P* Value
Inverse variance-weighted	1.085	1.033-1.140	0.001
Weighted median	1.045	0.982-1.111	0.164
MR-Egger (slope)	1.057	0.945-1.182	0.329
Analysis	**Intercept**	**95% Confidence Interval**	***P* Value**
MR-Egger (intercept)	1.003	0.992-1.014	0.608

AMD = age-related macular degeneration; D = diopter; MR = Mendelian randomization; OR = odds ratio.

TABLE 3. Sensitivity Analysis Results for Mendelian Randomization

Analysis[a]	Cause Effect (OR per D)	95% Confidence Interval	*P* Value
Inverse variance-weighted	1.069	1.016-1.124	0.010
Weighted median	1.046	0.980-1.117	0.175
MR-Egger (slope)	1.060	0.949-1.182	0.301
Analysis[a]	**Intercept**	**95% Confidence Interval**	***P* Value**
MR-Egger (intercept)	1.001	0.990-1.012	0.865

D = diopter; MR = Mendelian randomization; OR = odds ratio.
[a]Table data show sensitivity analysis results for Mendelian randomization analyses after excluding 31 variants strongly associated with nonrefractive error traits identified by Phenoscanner.

However, these explanations are not consistent with the frequently observed association between refractive error and early AMD as opposed to advanced AMD.[9,14,15]

Others, such as Pan and associates,[39] have discussed possible links between light exposure and refractive error, speculating that spectacle lens wear for refractive error may reduce UV exposure, although they noted that only a small proportion of their study sample classified as having either myopia or hyperopia did not wear spectacles. Furthermore, Quigley and associates[40] contended that spectacle lenses would have negligible filtering effect on the short wavelength visible light commonly linked to AMD risk. Quigley and associates[40] proposed that overall retinal light exposure using 2 sperate methods was demonstrated to increase with hyperopic refractive error (by proxy of axial eye length) was a more likely potential mechanism by which refractive error may be linked to increased risk of AMD.

In addition to arguments centering on the retina, a greater rigidity of the sclera in shorter, hyperopic eyes has also been proposed[14,39,41,42] as rigidity of the sclera has been identified as a risk factor in neovascular AMD.[43] Finally, myopic eyes characteristically have thinner choroids than hyperopic eyes.[44] Although this may imply that the choroidal contribution to removal of photoreceptor phagocytosis breakdown products may be relatively impaired in myopic eyes,[45] this is not borne out by the smaller size of drusen in myopic eyes.[46,47]

This work had a number of limitations. First, although steps were taken to minimize the risk of bias from the potential use of invalid instrumental variables (eg, due to horizontal pleiotropy) by performing MR-Egger, MR-PRESSO, and weighted median-based MR sensitivity analyses, such bias cannot be completely ruled out. Second, the assumption was made that there was a linear relationship between refractive error and the risk of AMD. Again, although observational studies of axial eye length (a surrogate for refractive error) and AMD risk suggest that this assumption was reasonable, data from a very large case-control sample with information on both AMD status and refractive error would be required to test it formally.[48] Third, with regard to the instrumental variable assumptions necessary for a valid MR analysis, all 126 genetic variants used demonstrated an association with refractive error in an independent replication sample (UK Biobank)

distinct from the discovery sample (CREAM and 23andMe). The variants together explained 4.4% of the variance in refractive error in an additional, independent sample of participants. Thus, the variants satisfied the first MR assumption of displaying robust association with the exposure. There was evidence of heterogeneity in the genetic variant-exposure versus genetic variant-outcome relationship (Q of 326.1; $I^2 = 61.6\%$) in the analysis using all 126 variants, suggesting that either the second and/or third MR assumptions were not met. The most likely reason for this was horizontal pleiotropy (ie, variants conferring a risk of AMD through a pathway other than through a direct effect on refractive error). Although the sensitivity analyses reduced the level of residual heterogeneity, they did not exclude it completely. However, the similarity in the causal effect estimates obtained with the original IVW MR analysis and the various sensitivity analyses provide reassurance that much of the original heterogeneity did not appreciably bias the results. However, as mentioned above, bias due to horizontal pleiotropy that was still present in all of our sensitivity analyses cannot be completely ruled out. Fourth, theoretically a 2-sample MR study design is at risk of confounding due to population stratification (if an instrumental variable tags groups of individuals with different ancestries and these groups differ in the prevalence of the outcome[16]). Because all 126 instrumental variables in the current study were associated with refractive error in UK Biobank participants carefully selected as having homogeneous European ancestry and association with AMD was also assessed in a sample restricted to those of European ancestry, the risk of confounding due to population stratification is extremely low.

In summary, MR analysis provided evidence that hyperopic eyes have an increased risk of AMD but that the causal effect size is modest (OR of 1.08 per D; $P = 0.007$). This degree of protection is consistent with that estimated in 2 large meta-analyses of cross-sectional and longitudinal observational studies (OR of 1.06-1.10 per D), which implies that confounder bias did not strongly impact previous risk estimates in these 2 studies. The increasing prevalence of myopia[49] and consequent reduction in the prevalence of hyperopia may serve to partially counter the higher incidence of AMD due to increased life expectancy[50] across most of the world. Nevertheless, this work emphasizes that risk factors other than refractive error, such as smoking, have a much greater impact on AMD risk.

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