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Exploring Effects of Age at the Onset of Myopia on Multiple Diseases Using Electronic Health Records

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Purpose: To examine whether genetic predisposition to age at the onset of myopia is associated with the development of future diseases.

Design: Mendelian randomization phenome-wide association study (MR-PheWAS) from the UK Biobank.

Participants: A polygenic risk score (PRS) for age at the onset of myopia was constructed using 80 variants selected from a genome-wide association study. Participants were eligible if they had available genetic information during recruitment between March 13, 2006, and October 1, 2010. Disease outcomes were mapped to phenotype codes (phecodes) based on hospital episode statistics and causes of death up to April 29, 2021.

Methods: The analysis of phenome-wide association studies (PheWAS) identified possible associations between the age of myopia-onset PRS and a range of disease outcomes. Cox proportional hazards analysis and 2-sample Mendelian randomization (MR) further confirmed associations between PRS and diseases passing Bonferroni correction. The disease-trajectory analysis explored the sequential patterns in childhood-onset and adult-onset groups.

Main Outcome Measures: Disease outcomes related to age at the onset of myopia.

Results: Our study population comprised 315 568 UK Biobank participants, and 1000 unique phecodes from 17 different disease categories were included for analysis. After Bonferroni correction, PheWAS identified younger age at myopia-onset PRS was associated with hospital-diagnosed myopia and 13 other outcomes when using the Bonferroni threshold (all $P < 5.0 \times 10^{-5}$). Eleven distinct disease associations with dose-response effects were confirmed using Cox proportional hazards analysis with stratified PRS. Two-sample MR analyses provided further support for the effects of younger age at myopia on higher risks of retinal detachments, cataracts, disorders of the vitreous body, and hypothyroidism, whereas older age of the onset of myopia conferred a higher risk of primary angle-closure glaucoma. Temporal analyses indicated myopia preceded the above disorders in both the childhood-onset and adult-onset groups.

Conclusions: This data-driven MR-PheWAS identified a range of ocular disorders and hypothyroidism that were related to age at the onset of myopia. Our results highlight the importance of treating younger-onset myopia and the management of myopia-related comorbidities.

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Myopia is an eye disease of axial length shortening that causes vision impairment if uncorrected. The disease is expected to affect 50% of the world's population by 2050 and poses a substantial economic burden worldwide.[1–3] Younger-onset myopia has been phenotypically linked with high myopia, which can lead to retinal detachment, glaucoma, progressive choroidal atrophy, blindness, and diminished quality of life.[4–9] Therefore, the age of the onset of myopia could serve as a crucial predisposing factor for various ocular conditions. However, most studies on this topic are observational in nature, leaving them vulnerable to reverse causation and residual confounding. Subsequently, the impact of age at the onset of myopia on commonly associated morbidities remains unclear.

Phenome-wide association studies (PheWAS) are a hypothesis-free approach to identifying novel age relationships at the onset of myopia based on large-scale electronic health records and remove much of the bias inherent within observational studies.[10,11] The addition of Mendelian randomization (MR), which employs genetic variants as instrumental variables, is also resistant to confounding associations or reverse causations.[12] Recent genome-wide

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association studies (GWAS) have led to major advances in understanding the effect of age at the onset of myopia on other diseases through the discovery of significantly associated loci.[13] These provide an unprecedented opportunity to apply these variants to an MR analysis and have previously confirmed relationships between diseases and their previously associated outcomes.[14–16] As age at the onset of myopia has only been associated via observational study data, the opportunity to confirm these outcomes will provide concrete evidence to support proactive efforts to reduce adverse outcome incidence.

In this study, Mendelian randomization phenome-wide association study (MR-PheWAS) was employed to comprehensively examine the impact of the onset of myopia age on health-related traits. A polygenic risk score (PRS) for the onset of myopia age based on an independent sample of 104 293 European-ancestry participants was constructed[13] and applied to each eligible individual within the UK Biobank cohort, which identified associations between PRS and a variety of diseases. These disease associations were validated via Cox proportional hazards analysis and 2-sample MR and temporally investigated for disease trajectory analyses.

Methods

Study Population

This registry-based case-control PheWAS was constructed using data from the UK Biobank, a prospective, population-based study that enrolled >500 000 participants aged between 37 and 73 years across 22 research centers in England, Scotland, and Wales.[17] All participants underwent comprehensive demographic and health assessments, provided biological samples, and consented to longitudinal follow-up during recruitment (between March 13, 2006, and October 1, 2010). This analysis used a subgroup of 315 568 unrelated White British individuals with available self-reported data and genetic information.

Ethical approval for the UK Biobank study was obtained from the National Information Governance Board for Health and Social Care and the North West Multicentre Research Ethics Committee (REC reference: 11/NW/0382). The current research was conducted under the UK Biobank application number 86091 in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent before data collection.

Phenome Generation

Disease outcome data were sourced through linkage to electronic health records and mortality registrations up to April 28, 2021. We extracted all entries according to the International Classification of Diseases, 9th/10th revision codes and converted them into phenotype codes (phecodes), which were closely aligned with diseases commonly used in clinical practice and genomics studies.[18] For each phecode, we coded individuals with the phecode as cases, while participants without the phecode in the same category were considered controls. For each PheWAS analysis, we excluded phecodes with <200 cases,[19] leaving 1000 unique phecodes for analyses.

To replicate MR-PheWAS findings on follow-up, we employed Cox proportional hazards regression analyses to confirm the relationships for the significant distinct outcomes that passed Bonferroni correction in the PheWAS. We converted the significant phecodes to International Classification of Diseases codes to identify the primary/secondary diagnoses in hospital admission data. The onset date was defined as the earliest recorded code date. Follow-up years were calculated from the date of baseline assessment to the date of onset, death, or the end of follow-up, whichever occurred first.

PRS of Age at Myopia Onset

Genotyping in the UK Biobank sample was performed using the Axiom or the Affymetrix array.[20] A PRS was constructed using 80 single-nucleotide polymorphisms (SNPs) previously identified as associated with self-reported age at myopia[13] ($P < 5 \times 10^{-8}$) by a recent meta-analysis of GWAS from 2 cohorts in 23andMe (Table S1, available at www.ophthalmologyscience.org). To avoid linkage disequilibrium bias, PLINK 1.9 clumped the genome-wide significant SNPs at an R^2 threshold of 0.001 within a 10 000 kilobase window. The classic thresholding and clumping method was applied to these variables, as described by an earlier paper.[21]

Measurements of Refractive Error and Age at Myopia Onset

At baseline, a subgroup of subjects from the UK Biobank undertook refractive error measurement using an autorefractor (Humphrey model 500, Humphrey Instruments). Refractive error was recorded regarding mean spherical equivalent (MSE) values for the 2 eyes. The spherical equivalent is calculated as equal to half of the cylinder power added to the spherical power and expressed in diopters (D). According to international guidelines, MSE <−1.0 D was identified as myopia, while MSE <−6.0 D was identified as high myopia.

The age at the onset of myopia was assessed using self-reported age at first glasses/contact lenses wear and the reason for first optical correction.[22] Participants in the UK Biobank were asked the following questions about optical correction: "Do you wear glasses or contact lenses to correct your vision? (yes, no, prefer not to answer)." If they answered "yes," they were asked, "At what age did you first start wearing glasses or contact lenses? (age in years, do not know, prefer not to answer)," and "Why were you prescribed glasses/contacts? (for short-sightedness, long-sightedness, astigmatism, etc.)."[22]

Demographic Data

Demographic information included age, sex, and the Townsend deprivation index. The ethnicity was self-reported and recorded as white and non-White (Asian, Black, Chinese, mixed, or other ethnic groups). Other covariates, including educational qualifications, smoking, alcohol consumption, and physical activity, were obtained through standardized questionnaires. Obesity was defined as body mass index >30 kg/m^2. Diabetes mellitus, hypertension, and hyperlipidemia were defined by self-report, diagnoses, medications, or physical measurements (Table S2, available at www.ophthalmologyscience.org).

Statistical Analysis

MR-PheWAS. Mendelian randomization PheWAS analysis was performed using the PRS as a continuous variable (per 1-standard deviation [SD] increment), with logistic regression employed to evaluate associations across 1000 distinct phecodes (modeled as binary outcomes). All models were adjusted for age, sex, Townsend index, educational qualifications, smoking status, alcohol consumption, obesity, physical activity, and the first 10 genetic

principal components. To account for multiple testing, we implemented both Bonferroni correction (significance threshold $P < 5.0 \times 10^{-5}$, derived from $\alpha = 0.05$ divided by 1000 tests) and false discovery rate control (<0.0011). Additionally, we quantified the proportion of variance in refractive error explained by the age at the onset of myopia PRS by computing the incremental R^2 (coefficient of determination) in linear regression models.

Cox Proportional Hazard Regression. Cox proportional hazard regression models examined the association between age at the onset of myopia PRS and incident outcomes that passed Bonferroni correction in the PheWAS. The PRS values were stratified into tertiles (low, medium, and high) to evaluate potential dose-dependent associations, with corresponding hazard ratios and 95% confidence intervals (CIs) calculated.

Two-Sample MR Analyses. For the significant distinct outcomes that passed Bonferroni correction in the PheWAS, we further replicated their causal associations using 2-sample MR analyses based on previous GWAS for age at the onset of myopia as described earlier and GWAS for each outcome conducted in the UK Biobank using the same phecode identified in the PheWAS.[23] Genetic instruments for age at the onset of myopia were chosen with a threshold of 5×10^{-8} using previous GWAS summary statistics described earlier. These SNPs were clumped with a distance of 3000 kb and a maximum linkage disequilibrium r^2 of 0.001 to ensure they were each independent. We used the inverse-variance weighted method for our main analyses and the MR-Egger, weighted median, weighted mode, and MR pleiotropy residual sum and outlier (MR-PRESSO) as sensitivity analyses for exploring potential bias due to unbalanced horizontal pleiotropy. The MR-PRESSO method additionally provides 3 informative tests: a global test to detect the presence of pleiotropy, an outlier test to detect potentially pleiotropic outlier variants, and a distortion test to identify changes in the causal estimates after exclusion of the pleiotropic outlier variants.[24]

Disease-Trajectory Analyses. Disease-trajectory analyses were further conducted to test whether the sequential patterns of multiple morbidities related to myopia between different age groups of the onset of myopia are different. We included distinct outcomes that passed Bonferroni correction in the PheWAS and 2-sample MR analyses.

All statistical analyses were conducted using Stata version 16.0 (StataCorp) and R (version 3.3.0, R Foundation for Statistical Computing, www.R-project.org). All P were 2-sided with statistical significance set at <0.05.

Results

The study population comprised 315 568 adults with genetic information at a mean age of 57 years (SD = 8), and 53.7% (n = 169 442) were women. In a subset of 71 688 participants with MSE measurements, the mean value of spherical equivalent was −0.34 D (SD = 2.72 D) with a range of −22.60 D to +13.96 D. The prevalence of myopia with MSE ≤−1 D was 27.76% (n = 19 901), and high myopia with MSE ≤−6.0 D was 4.05% (n = 2905). Of participants with recorded age at the onset of myopia (n = 39 999), the median onset age was 17 years (interquartile range 12−30, range 1−77 years). Individuals with younger age at the onset of myopia (<18 years) were more likely to be female, with lower socioeconomic status, highly educated, nonsmokers, not obese, and have a higher degree of myopia (Table 1). The flowchart of participant recruitment is shown in Figure S1 (available at www.ophthalmologyscience.org).

The age at the onset of myopia genetic risk score included 80 SNPs and explained 1.10% of the variance in age at the onset of myopia. Coefficients for the effect of each SNP on age at the onset of myopia are listed in Table S1. In our PheWAS encompassing 1000 unique phecodes across 17 disease categories (Table S3, available at www.ophthalmologyscience.org), the strongest association emerged between the PRS and myopia (odds ratio [OR] = 0.41, 95% CI = 0.36−0.46, $P = 4.19 \times 10^{-52}$), corresponding to a 59% reduction in myopia odds per 1-SD increase in PRS. Additionally, we identified significant associations with 13 other phecodes that survived Bonferroni correction (all $P < 5.0 \times 10^{-5}$; Fig 1, Table 2). Negative associations with genetic risk scores of age at the onset of myopia were significant for cataracts (OR = 0.82, 95% CI = 0.79−0.84, $P = 1.19 \times 10^{-38}$), retinal detachments (OR = 0.59, 95% CI = 0.55−0.64, $P = 1.75 \times 10^{-37}$), blindness and low vision (OR = 0.64, 95% CI = 0.59−0.70, $P = 3.29 \times 10^{-23}$), disorders of the vitreous body (OR = 0.68, 95% CI = 0.60−0.76, $P = 1.04 \times 10^{-10}$), and macular degeneration of the retina (OR = 0.82, 95% CI = 0.76−0.89, $P = 5.23 \times 10^{-06}$), whereas primary angle-closure glaucoma (PACG) was positively associated (OR = 1.94, 95% CI = 1.67−2.27, $P = 3.19 \times 10^{-17}$). Two phecodes from digestive and endocrine/metabolic disease groups were uniquely associated with risk scores of age at the onset of myopia and included celiac disease (OR = 0.71, 95% CI = 0.64−0.78, $P = 3.69 \times 10^{-11}$) and hypothyroidism (OR = 0.92, 95% CI = 0.89−0.95, $P = 9.51 \times 10^{-06}$). Age at myopia PRS passed false discovery rate correction for diabetes mellitus−related phecodes and cystic mastopathy but did not pass Bonferroni thresholds (Table 2).

Next, dose-response associations between age at myopia PRS and previously significant disorders were investigated using the Cox proportional hazard regression models over a median follow-up of 12.2 years (interquartile range 11.5−12.9). Hazard ratios for risks of these disorders stratified by PRS tertiles are shown in Figure 2 and Table S4 (available at www.ophthalmologyscience.org). Compared with the lowest PRS quartile, higher age at myopia PRS was significantly associated with decreased risk of retinal detachments, cataracts, disorders of the vitreous body, celiac disease, and hypothyroidism (all P for trend <0.01), but conferred an increased risk of primary angle-closure glaucoma (P for trend <0.001). A sensitivity analysis was applied to hypothyroidism by introducing hypothyroidism-related medication as the outcome. Subsequently, age at the onset of myopia PRS was significantly associated with the use of hypothyroidism-related medication after adjustment for the covariates (hazard ratio = 0.96, 95% CI = 0.93−0.99, $P = 0.014$).

After removing overlapping phecodes, the 2-sample MR analysis showed associations between age at the onset of myopia and 5 distinct conditions that passed Bonferroni correction (Fig 3). These conditions included cataracts, retinal detachments, PACG, disorders of the vitreous body, and hypothyroidism. Genetic evidence supported that younger age at the onset of myopia was associated with a higher risk of retinal detachments, cataracts,

Table 1. Demographic Characteristics of Participants with Baseline Reported Age at the Onset of Myopia

Baseline Characteristic	Total	Age at the Onset of Myopia		P Value
		Age <18 years	*Age ≥18 years*	
N	39 999	20 778	19 221	-
Age, mean (SD), yrs	56.29 (7.84)	56.24 (7.70)	55.35 (7.98)	**<0.001**
Sex, no. (%)				
Female	21 026 (52.57)	11 752 (56.56)	9274 (48.25)	**<0.001**
Male	18 973 (47.43)	9026 (43.44)	9947 (51.75)	
Townsend index, mean (SD)	−1.46 (2.81)	−1.44 (2.82)	−1.49 (2.81)	**0.049**
Education level, no. (%)				
College or university degree	18 878 (47.20)	11 261 (54.20)	7617 (39.63)	**<0.001**
Others	21 121 (52.80)	9517 (48.80)	11 604 (60.37)	
Smoking status, no. (%)				
Never	23 413 (58.66)	12 513 (60.31)	10 900 (56.87)	**<0.001**
Former/current	16 499 (41.34)	8234 (39.69)	8265 (43.13)	
Drinking status, no. (%)				
Never	1094 (2.74)	564 (2.72)	530 (2.76)	0.79
Former/current	38 889 (97.26)	20 207 (97.28)	18 682 (97.24)	
Obesity, no. (%)				
No	31 366 (78.72)	16 457 (79.50)	14 909 (77.87)	**<0.001**
Yes	8481 (21.28)	4243 (20.50)	4238 (22.13)	
Physical activity, no. (%)				
Not meeting recommendation	6370 (18.72)	3354 (19.08)	3016 (18.34)	0.08
Meeting recommendation	27 649 (81.28)	14 222 (80.92)	13 427 (81.66)	
History of diabetes, no. (%)				
No	37 901 (94.75)	19 741 (95.01)	18 160 (94.48)	**0.018**
Yes	2098 (5.25)	1037 (4.99)	1061 (5.52)	
History of hypertension, no. (%)				
No	11 304 (28.26)	6098 (29.35)	5206 (27.08)	**<0.001**
Yes	28 695 (71.74)	14 680 (70.65)	14 015 (72.92)	
History of hyperlipidemia, no. (%)				
No	22 362 (55.91)	11 738 (56.49)	10 624 (55.27)	**0.014**
Yes	17 637 (44.09)	9040 (43.51)	8597 (44.73)	
MSE, mean (SD)	−2.39 (2.93)	−3.61 (3.05)	−1.07 (2.12)	**<0.001**

MSE = mean spherical equivalent; SD = standard deviation.
Bold font denotes significance at the 0.05 level.

disorders of the vitreous body, and hypothyroidism, while older age at myopia with a higher risk of PACG with >3 of the 5 methods. A sensitivity analysis assessing pleiotropy and stability of estimation via the MR-Egger pleiotropy test indicated directional pleiotropy for age at the onset of myopia and retinal detachment ($P = 0.017$).

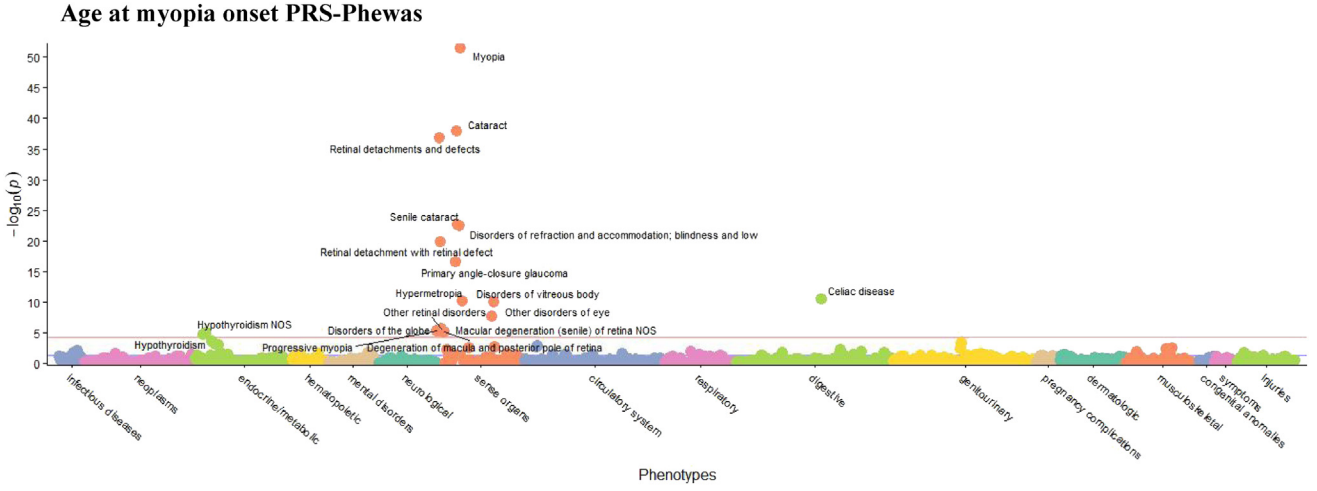

Figure 1. Manhattan plot showing the phenome-wide association between age at the onset of myopia PRS and disease outcomes. Bonferroni-corrected threshold ($P < 5.0 \times 10^{-5}$) is represented by the red line. The PheWAS model was adjusted for age, sex, BMI, Townsend index, smoking status, and education status. BMI = body mass index; NOS = not otherwise specified; PheWAS = phenome-wide association study; PRS = polygenic risk score.

Table 2. Disease Outcomes Identified in the PheWAS of Age at the Onset of Myopia Genetic Risk Score under FDR-Corrected Thresholds

Phecode	Description	Group	OR	95% CI	*P* Value	Under Bonferroni Corrected Thresholds
367.1	Myopia	Sense organs	0.41	0.36–0.46	4.19×10^{-52}	YES
366	Cataract	Sense organs	0.82	0.79–0.84	1.19×10^{-38}	YES
361	Retinal detachments and defects	Sense organs	0.59	0.55–0.64	1.75×10^{-37}	YES
366.2	Senile cataract	Sense organs	0.80	0.76–0.83	2.35×10^{-23}	YES
367	Disorders of refraction and accommodation; blindness and low vision	Sense organs	0.64	0.59–0.70	3.29×10^{-23}	YES
361.1	Retinal detachment with retinal defect	Sense organs	0.57	0.51–0.64	1.45×10^{-20}	YES
365.2	Primary angle-closure glaucoma	Sense organs	1.94	1.67–2.27	3.19×10^{-17}	YES
557.1	Celiac disease	Digestive	0.71	0.64–0.78	3.69×10^{-11}	YES
379.2	Disorders of vitreous body	Sense organs	0.68	0.60–0.76	1.04×10^{-10}	YES
379	Other disorders of eye	Sense organs	0.81	0.75–0.87	2.28×10^{-08}	YES
362	Other retinal disorders	Sense organs	0.84	0.79–0.91	2.29×10^{-06}	YES
360.2	Progressive myopia	Sense organs	0.51	0.38–0.68	3.83×10^{-06}	YES
362.2	Degeneration of macula and posterior pole of retina	Sense organs	0.82	0.76–0.90	5.78×10^{-06}	YES
244	Hypothyroidism	Endocrine/metabolic	0.92	0.89–0.96	1.61×10^{-05}	YES
250	Diabetes mellitus	Endocrine/metabolic	0.94	0.91–0.97	2.06×10^{-04}	NO
250.1	Type 1 diabetes	Endocrine/metabolic	0.85	0.78–0.93	2.88×10^{-04}	NO
610.1	Cystic mastopathy	Genitourinary	1.30	1.12–1.51	4.82×10^{-04}	NO
250.13	Type 1 diabetes with ophthalmic manifestations	Endocrine/metabolic	0.70	0.57–0.86	6.70×10^{-04}	NO
250.2	Type 2 diabetes	Endocrine/metabolic	0.95	0.91–0.98	1.07×10^{-03}	NO

CI = confidence interval; FDR = false discovery rate; OR = odds ratio; PheWAS = phenome-wide association study.
The PheWAS model was adjusted for age, sex, obesity, Townsend index, smoking status, and education status.

Additionally, significant heterogeneity was detected between age at myopia, cataract, and PACG for inverse-variance weighted and MR Egger models ($P < 0.05$). The MR-PRESSO test also identified outlying variants for cataracts, disorders of the vitreous body, age-related macular degeneration, and hypothyroidism; however, excluding these variants did not significantly affect effect estimates (for all mentioned above, P distortion >0.45).

Temporal analyses were conducted between myopia and traits, which showed genetic evidence between the time of diagnosed cataracts, retinal detachment, PACG, disorders of the vitreous body, and hypothyroidism relative to age at the diagnosis of myopia (Fig 4). Patients with childhood-onset myopia (diagnosed before 18 years of age) exhibited a substantially longer mean interval preceding these comorbidities (50.65 years, SD 2.55) compared with those with adult-onset myopia (diagnosed at 18 years or later), who developed complications after a mean of 15.38 years (SD 3.96). In sensitivity analyses stratifying participants into early-onset (diagnosed before 12 years) and late-onset (diagnosed after 12 years) myopia subgroups, Figure S2 (available at www.ophthalmologyscience.org) demonstrates this temporal pattern was similar, with early-onset cases showing a mean lead time of 53.36 years (SD 3.93) versus 20.18 years (SD 5.05) for late-onset cases.

Discussion

This data-driven MR-PheWAS offers evidence that a younger-onset of myopia is linked to ocular disorders and hypothyroidism development. Herein, >315 000 participants from the UK Biobank were analyzed according to a PRS-based PheWAS, followed by Cox proportional hazards analysis using follow-up data and 2-sample MR analysis. These rigorous methods consistently supported associations of younger-onset of myopia age with cataracts, retinal detachments, PACG, vitreous body disorders, and hypothyroidism risk. These findings solidify previous associations with a robust relationship and emphasize the importance of slowing myopia progression in children and teenagers to prevent vision impairment and other adverse outcomes.[25,26]

Population-based observational studies have previously documented that younger-onset myopia is associated with the development of future ocular disorders, but genetic associations have not been identified until now. Childhood-onset myopia is thought to increase the risk of complications that stem from thinning of the eyeball with excessive elongation, which include nuclear and posterior subcapsular cataracts, disorders of the vitreous body, retinal detachment, and myopic macular degeneration.[27–31] This MR-PheWAS analysis still identified these as complications of younger-onset myopia despite the hypothesis-free design of the study, confirming these outcomes. Longitudinal associations between the age of the onset of myopia and the significant ocular disorders had dose-response associations, suggesting these were outcomes of long-standing disease. This was also true for PACG, where myopia was protective for its development, consistent with previous studies showcasing this association,[32,33] which likely results from the deeper anterior chamber depth, larger anterior chamber volumes, and longer axial lengths present in myopia. Still, directionally opposite

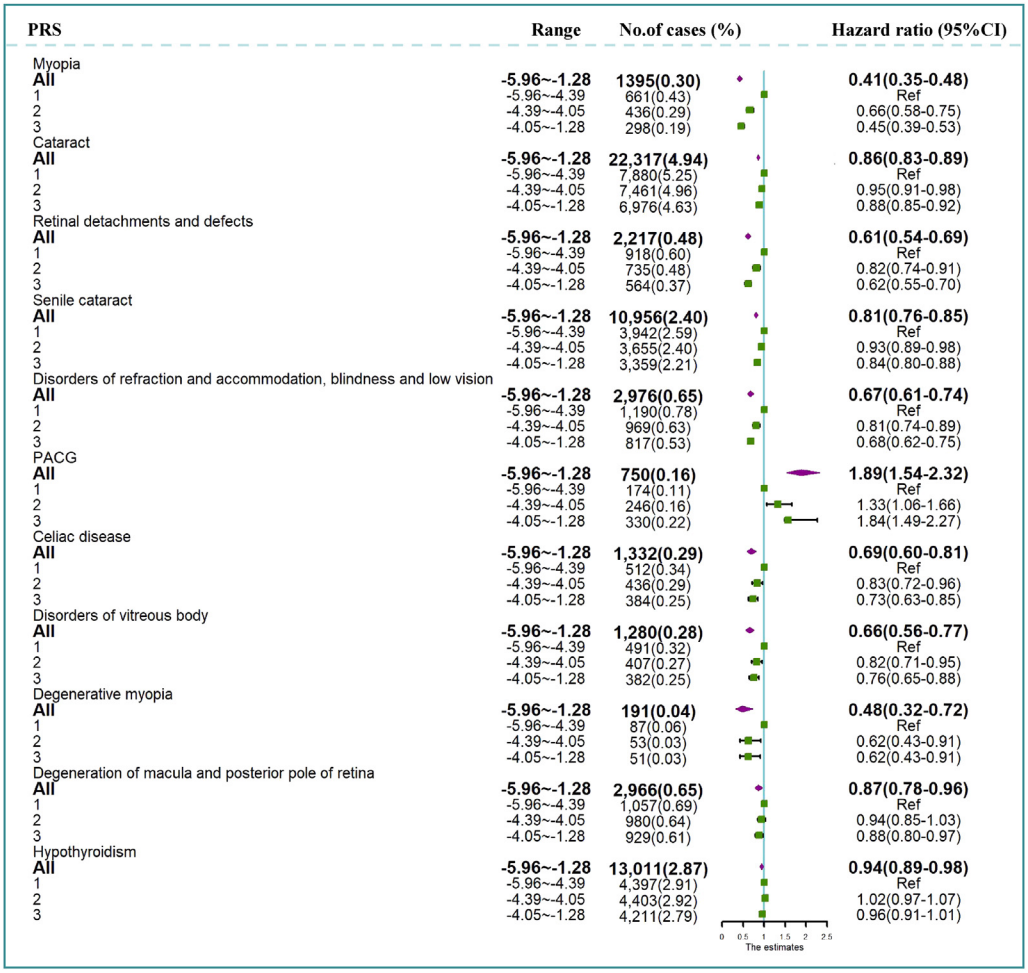

Figure 2. Forest plot showing phenotypes significantly associated with age at the onset of myopia PRS, grouped by categories. The hazard ratio (95% CI) for each phenotype was estimated by Cox proportional hazard regression. CI = confidence interval; PACG = primary angle-closure glaucoma; PRS = polygenic risk score.

effects of myopia on PACG have been observed, which could stem from myopia-associated enlargement of the optic disc,[34] and the secondary stretching and thinning of the lamina cribrosa in association with pronounced changes in the biomechanics of the optic nerve head.[35] In contrast to PACG, MR-PheWAS analysis revealed no significant association between PRS for age at the onset of myopia and primary open-angle glaucoma after false discovery rate correction. Further investigations with larger sample sizes are needed to evaluate the risks of glaucoma-related biomechanical and microstructural changes in both childhood-onset and late-onset myopia groups.

The reported association of younger-onset myopia with hypothyroidism is relevant to findings from previous case reports showing their incidental comorbidity,[36,37] although other evidence supporting this association is not yet published. While this study provides genetic evidence for the relationship between the onset of myopia age and hypothyroidism as well as thyroxine use, this should also be true for people with thyroidectomies, which also require hormone replacement. As such, the association of myopia with other thyroid abnormalities should be considered by future studies, as it is unclear why these were not associated in the MR-PheWAS herein.

This study investigated relationships between age at the onset of myopia and associations that passed Bonferroni corrections in PheWAS. Two-sample MR analyses verified associations between the onset of myopia age and cataracts, retinal detachments, PACG, and disorders of the vitreous body. However, previous studies have also suggested these relationships could be influenced by pleiotropy for cataracts, disorders of the vitreous body, and age-related macular degeneration.[38–40] Therefore, MR-PRESSO analysis excluded potentially pleiotropic variants, and the resulting effect was not notably affected. In contrast, 2-sample MR methods revealed limited evidence for the causal effects of age at the onset of myopia on macular degeneration and celiac disease. Other confounding factors may explain their relationships. On the other hand, robust MR estimates confirmed the relationship between age at the onset of myopia and hypothyroidism without any pleiotropy effects.

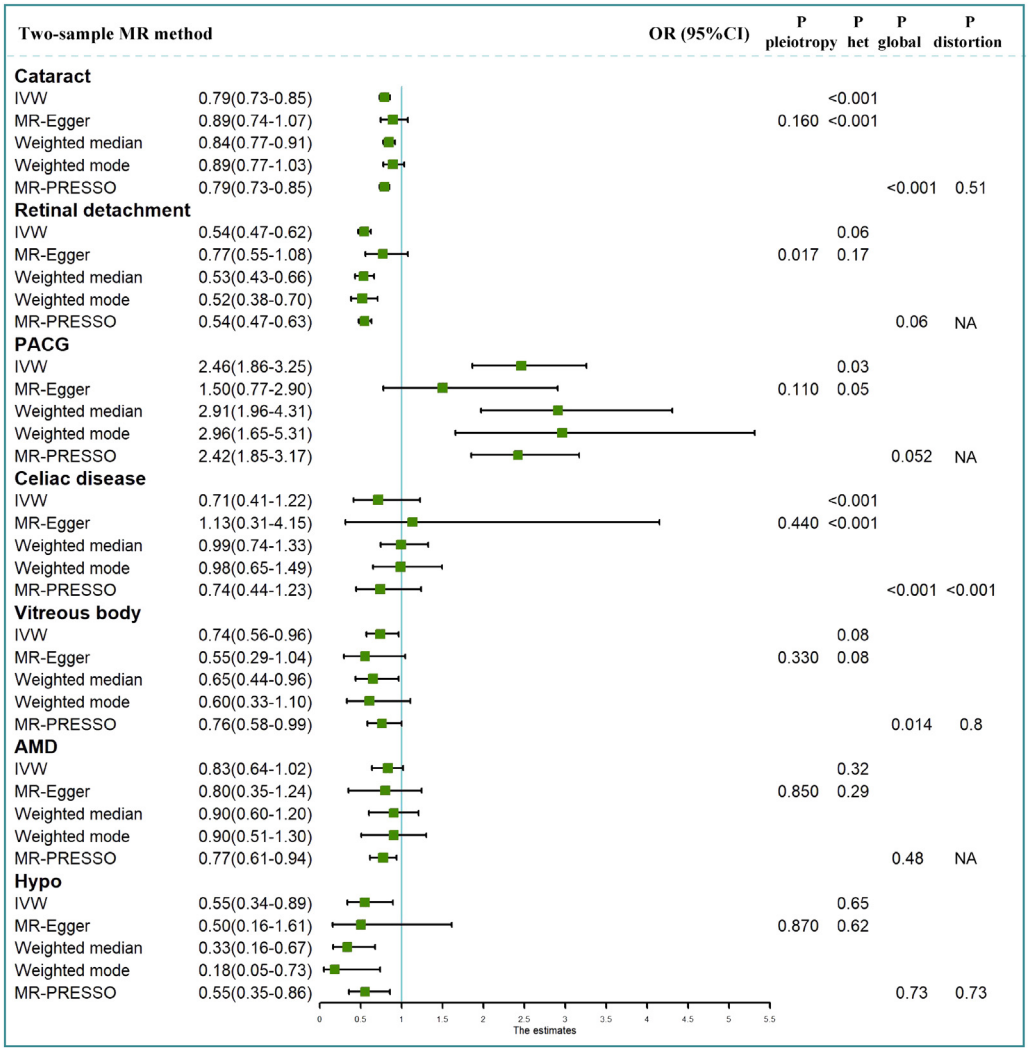

Figure 3. Two-sample Mendelian randomization analyses on the 7 distinct outcomes significantly associated with age at the onset of myopia PRS at Bonferroni-corrected significant threshold. The OR (95% CI) for each phenotype was estimated by 5 2-sample Mendelian randomization analyses. The MR-Egger intercept test ($P_{pleiotropy}$) and MR-PRESSO global test (P_{global}) indicate whether there is no horizontal pleiotropy. The MR-PRESSO distortion test ($P_{distortion}$) indicates whether the causal estimate is significantly affected by the removal of pleiotropic variants. AMD = age-related macular degeneration; CI = confidence interval; IVW = inverse-variance weighted; MR = Mendelian randomization; MR-PRESSO = Mendelian randomization pleiotropy residual sum and outlier; OR = odds ratio; PACG = primary angle-closure glaucoma; PRS = polygenic risk score.

The temporal analysis paid close attention to age distributions of various morbidities related to the onset of myopia in childhood and adult-onset groups. This information provides temporal information about disease associations and suggests myopia diagnosis precedes other ocular disorders. While this has been presumed in the past, confirming this information provides a new impetus to structure intervention time points to prevent the development of myopia-related comorbidities. The timing of myopia-treating interventions should be paid attention to in future study designs to ensure vision specialists are providing optimal care and provide evidence current guidelines for myopia interventions are aligned with better long-term outcomes.

The strengths of this study include its large sample size, comprehensive data on hospitalization and mortality registrations, and minimal selection bias. As the first MR-PheWAS analysis to examine associations related to the age of the onset of myopia, these findings are novel and confirmed by rigorous methods that constructed a PRS based on previous GWAS, an MR approach, and longitudinal analyses to evaluate for relationships between myopia and traits of interest. Despite these findings, some limitations should also be acknowledged. First, the GWAS that informed our PRS relied on self-reported age of the onset of myopia, which may be inaccurate and could introduce bias. Second, as the UK Biobank used hospitalization and mortality data at follow-up, the diagnosis of ocular diseases and hypothyroidism was limited to hospitals, while in reality, many illnesses are diagnosed in-clinic. Third, the older baseline age of this study population restricts the generalizability of our findings to younger individuals. However, these findings remain valuable for expanding an

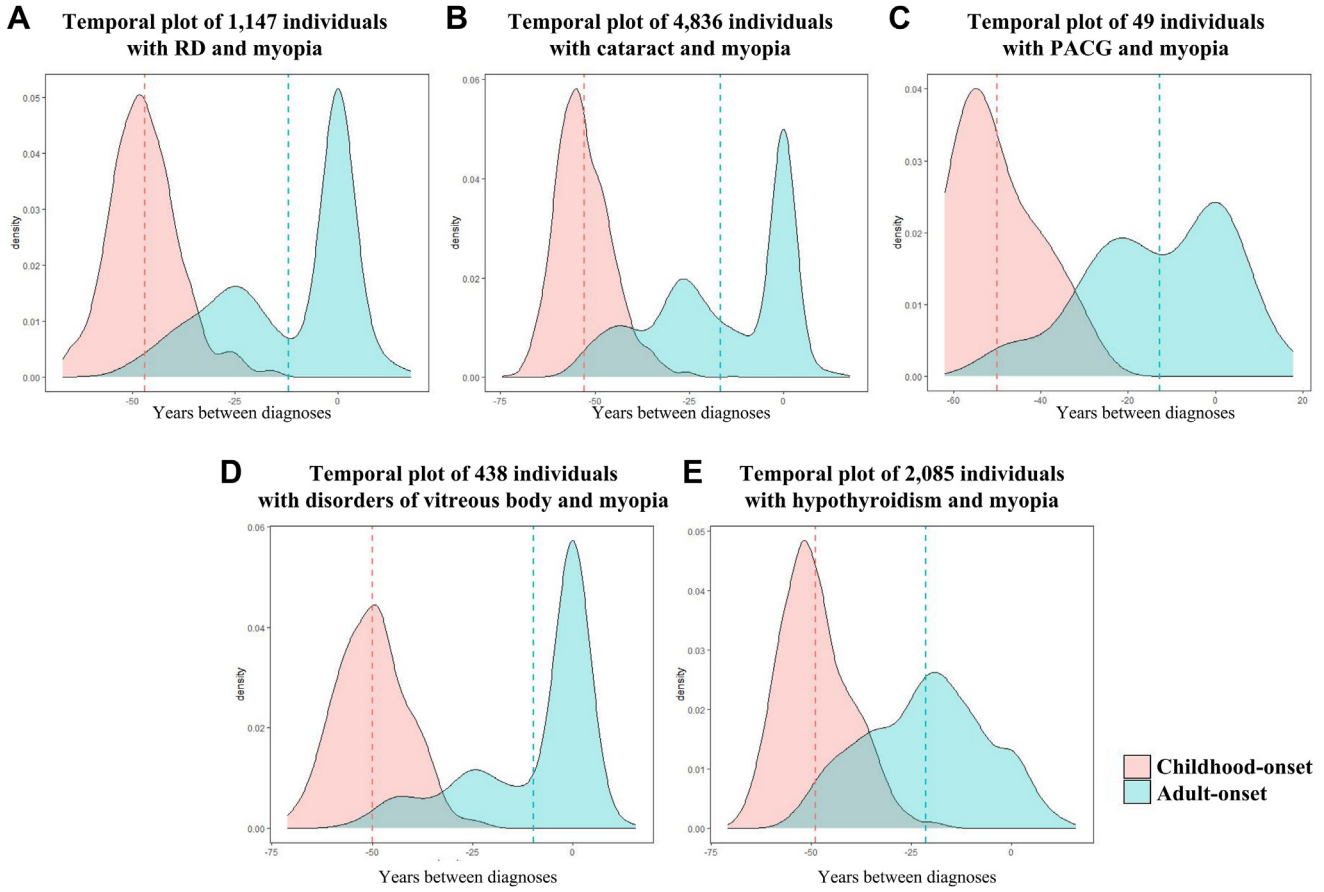

Figure 4. Temporal order of diagnoses. **A,** Distribution of years between the onset of myopia and RD onset for patients with childhood-onset myopia (≤18 years, pink) and for patients with adult-onset myopia (>18 years, blue). **B,** Distribution of years between the onset of myopia and cataract onset. **C,** Distribution of years between the onset of myopia and PACG onset. **D,** Distribution of years between the onset of myopia and disorders of vitreous body onset. **E,** Distribution of years between the onset of myopia and hypothyroidism onset. The x-axis represents years between myopia and subsequent comorbidities diagnosis. Dashed lines indicate mean intervals for each group. PACG = primary angle-closure glaucoma; RD = retinal detachment.

understanding of this topic. Finally, although we employed a rigorous modeling strategy for the 2-sample MR analysis, bias stemming from pleiotropic effects cannot be completely ruled out from residual confounding, which may introduce positive or negative bias for estimated effect sizes and even lead to reverse causality.[41]

Conclusion. This MR-PheWAS produced robust and well-powered causal insights into the effects of age at the onset of myopia on various diseases. Our results emphasize that younger-onset myopia is a significant public health concern for an ethnically diverse and aging population. These findings offer a foundation for further research on the prevention of myopia and its causally related comorbidities.

Availability of Data and Materials

All data are available through the UK Biobank repository on the application. All code for the statistical analyses is available from the corresponding author.

Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. Ethics approval for the UK Biobank was granted by the National Information Governance Board for Health and Social Care and the North West Multicentre Research Ethics Committee (11/NW/0382). All research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

No animal subjects were used in this study.

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Analysis and interpretation: Zhang, Yu

Obtained funding: Zhang, Yu

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Abbreviations and Acronyms:
CI = confidence interval; **D** = diopters; **GWAS** = genome-wide association studies; **MR** = Mendelian randomization; **MR-PheWAS** = Mendelian randomization phenome-wide association study; **MR-PRESSO** = Mendelian randomization pleiotropy residual sum and outlier; **MSE** = mean spherical equivalent; **OR** = odds ratio; **PACG** = primary angle-closure glaucoma; **PheWAS** = phenome-wide association studies; **PRS** = polygenic risk score; **SD** = standard deviation; **SNP** = single-nucleotide polymorphism.

Keywords:
Age at myopia onset, Phenome-wide association study, Mendelian randomization, Myopia-related comorbidities.

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