Exploring the Relationship Between Refractive Errors and Common Chronic Diseases Via Blood Biochemistry Tests: A Large Prospective Cohort Study

Yanze Yu,[1–3] Hao Chen,[4] Zhanying Wang,[1–3] Yuhao Ye,[1–3] Zhe Zhang,[1–3] Yongle Bao,[1–3] Yingnan Jia,[4] Xingtao Zhou,[1–3] and Jing Zhao[1–3]

[1]Department of Ophthalmology and Vision Science, Eye and ENT Hospital, Fudan University, Shanghai, China
[2]NHC Key Laboratory of Myopia and Related Eye Diseases, Shanghai, China
[3]Key Laboratory of Myopia and Related Eye Diseases, Chinese Academy of Medical Sciences, Shanghai, China
[4]Department of Preventive Medicine and Health Education, School of Public Health, Fudan University, Shanghai, China

Correspondence: Jing Zhao, Department of Ophthalmology and Vision Science, Eye and ENT Hospital, Fudan University; NHC Key Laboratory of Myopia and Related Eye Diseases; Key Laboratory of Myopia and Related Eye Diseases, Chinese Academy of Medical Sciences, 83 Fenyang Rd., Shanghai 200031, China; zhaojing_med@163.com.
Xingtao Zhou, Department of Ophthalmology and Vision Science, Eye and ENT Hospital, Fudan University; NHC Key Laboratory of Myopia and Related Eye Diseases; Key Laboratory of Myopia and Related Eye Diseases, Chinese Academy of Medical Sciences, 83 Fenyang Rd., Shanghai 200031, China; doctzhouxingtao@163.com.
Yingnan Jia, Department of Preventive Medicine and Health Education, School of Public Health, Fudan University, 138 Yixueyuan Rd., Shanghai 200031, China; jyn@fudan.edu.cn.

YY, HC, and ZW contributed equally to this manuscript.

Received: May 31, 2024
Accepted: September 6, 2024
Published: November 14, 2024

Citation: Yu Y, Chen H, Wang Z, et al. Exploring the relationship between refractive errors and common chronic diseases via blood biochemistry tests: A large prospective cohort study. *Invest Ophthalmol Vis Sci.* 2024;65(13):26. https://doi.org/10.1167/iovs.65.13.26

Purpose. The purpose of this study was to examine the association between refractive errors and common chronic diseases using blood biochemistry tests, and to investigate the associated modifiable risk factors, with the goal of informing and developing effective preventive strategies.

Methods. A total of 116,245 participants with refractometry at baseline enrolled in the UK Biobank were included in this prospective cohort study. Restricted cubic spline and Cox proportional hazards models were used to detect associations between refractive error, blood biochemistry tests, and common chronic diseases. Interaction effects on the additive scale and effect modification analysis were used to explore excess modifiable risk factors for disease prevention.

Results. Spherical equivalent significantly associated with vitamin D, sex hormone binding globulin, apolipoprotein A, blood glucose, and aspartate aminotransferase levels. Subjects with myopia demonstrated a 13% higher risk of type 2 diabetes mellitus (T2DM) incidence compared to those without myopia (hazard ratio [HR] = 1.13, 95% confidence interval [CI] = 1.08–1.19) throughout a median follow-up of 9.12 years. Interaction analysis revealed 15% (95% CI = 9%–21%) of this risk was due to myopia-obesity interaction. However, active engagement in physical activity could potentially mitigate this risk (HR = 1.06, 95% CI = 0.93–1.20).

Conclusions. Refractive errors were associated with specific blood indicators, particularly noting the association between myopia and higher T2DM incidence in middle-aged and elderly populations. This effect interacts with obesity, and promoting physical activity among myopia individuals provides greater benefits in the prevention of T2DM compared to non-myopic individuals.

Keywords: refractive errors, chronic diseases, myopia, type 2 diabetes mellitus (T2DM), physical activity

In the vast tapestry of human health, the complex interplay among seemingly distinct physiological systems continues to intrigue researchers. A compelling area of exploration is the correlation between ocular conditions and common chronic diseases.[1] Recent studies have explored this relationship, suggesting that ocular conditions may significantly impact overall systemic well-being.[2–8] For instance, cardiovascular disease, which includes conditions like coronary artery disease and heart failure, often coexists with ocular issues like glaucoma and macular degeneration.[2,6,8] However, refractive errors, including myopia, hyperopia, and astigmatism, are acknowledged as the primary drivers

of global visual impairment, accounting for 123.7 million instances of moderate to severe distance vision impairment or blindness.[9–11] Although refractive errors typically stabilize after early adulthood, persisting as long-term conditions,[12] their associations with common chronic diseases remain poorly understood. Investigating these associations may reveal important insights into how refractive errors could be linked with or influence the progression of chronic diseases, potentially guiding preventive strategies and interventions.

This study used data from the UK Biobank (UKB) to comprehensively investigate refractive errors' potential predisposition to systemic disorders. Using a prospective cohort design with a substantial sample size of 116,245 individuals, we aimed to provide robust insights into human health. Specifically, we elucidated the intricate associations between refractive errors and common chronic diseases using key blood biochemical markers. Our secondary aim was to identify modifiable factors and assess the excess risk of interaction effects that could potentially mitigate or exacerbate the adverse effects associated with refractive errors.

Methods

Data Source and Study Population

The UKB is a substantial, prospective cohort study comprising >500,000 individuals aged 40 to 69 years across the United Kingdom.[13] These participants were recruited from 22 assessment centers nationwide, each registered under the UK National Health Service (NHS), ensuring comprehensive long-term monitoring. Ethical approval was granted by the National Information Governance Board for Health and Social Care and the NHS North West Multi-Center Research Ethics Committee.[14] Prior to enrollment, all participants provided informed consent electronically. This study was conducted in accordance with the UKB application number 105765 and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies. Participants were prospectively enrolled from the pool of UKB data, which was collected from across 22 assessment centers between 2006 and 2010. These individuals were invited to participate during routine clinic visits as part of the UKB recruitment process. Initially, we included UKB participants with refractometry results (n = 130,475). Subsequently, we excluded those lost to follow-up (n = 10,624), individuals with missing covariate data (n = 1786), and 1820 participants with outlier spherical equivalent (SE) values (see "Refractometry and myopia diagnosis" section). This process yielded a final cohort of 116,245 participants for the main analysis (Fig. 1). Detailed information on the variable definitions is provided in Supplementary Tables S1 and S2 and Supplementary Methods.

Statistical Analysis

The study initially compared baseline characteristics between male and female participants, reporting continuous variables as means (standard deviation [SD]) and categorical variables as numbers (percentages). For the main analysis, we utilized restricted cubic spline (RCS) models with five knots to assess both linear and nonlinear relationships between SE and each biochemical parameter. To further validate these associations and fully detect the complex nature of the relationships between SE and blood biochemistry

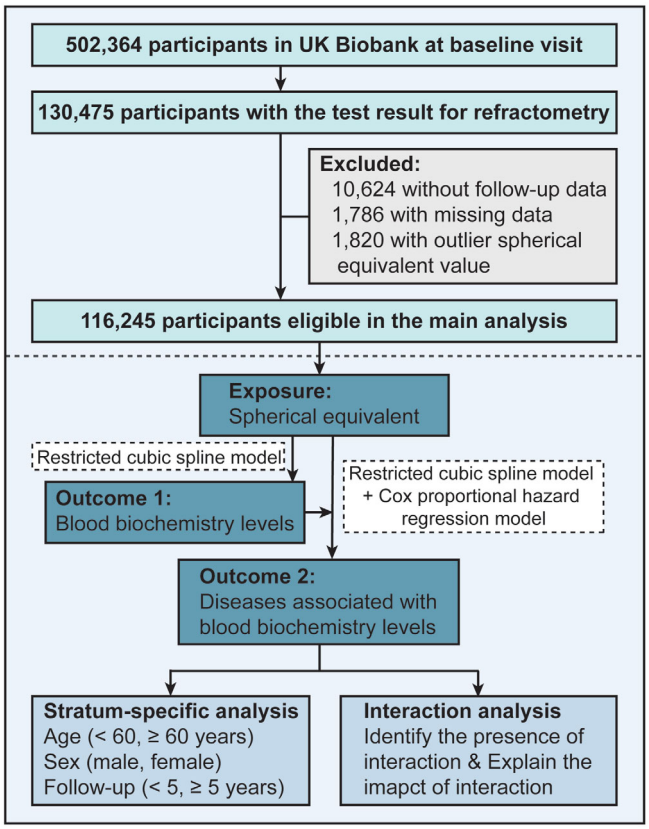

Figure 1. Flow chart of the study design. Flow chart depicting the criterion of the study cohort from participants in the UK Biobank and analytic approach of this study in detail.

tests,[15] we performed stratum-specific analyses based on age at baseline (≤60 and >60 years) and sex (male and female) for the nonlinearity associations. In model I, adjustments were made for age, sex, ethnicity, education level, Townsend deprivation index, and body mass index (BMI). In model II, the primary model selected for analysis and presentation, included additional adjustments for smoking status, alcohol consumption status, and history of hypertension and diabetes. All covariates in this study were based on baseline data.

Furthermore, we utilized RCS models integrated into Cox proportional hazard (CPH) models with five knots to flexibly model and depict the relationship between SE and the incidence of osteoporosis, hyperlipidemia, type 2 diabetes mellitus (T2DM), and chronic liver disease during the follow-up. These spline models were adjusted for the same covariates as described in model II. To evaluate potential nonlinearity in the associations, we conducted a likelihood ratio test by comparing models containing solely linear terms against those incorporating both linear and cubic spline terms.

In the sensitivity analyses, we first segmented SE to confirm its association with incident T2DM and identify the effect of each 1 diopter (D) increment in SE on T2DM incidence, as well as whether the presence of myopia influenced T2DM incidence. Myopia was defined as SE ≤ −0.75 D. Subsequent stratum-specific analyses were carried out to replicate the associations observed in the preceding step. These analyses were stratified by age at base-

line (≤60 and >60 years), sex (male and female), and follow-up time (≤5 and >5 years) to ensure the robustness of our findings. Additionally, we assessed the additive interaction between myopia (absent versus present) and obesity (BMI < 30 kg/m^2 versus BMI ≥ 30 kg/m^2) using three metrics: relative excess risk due to interaction (RERI), attributable proportion (AP), and the synergy index (SI).[16] This evaluation was performed using the following formulas:

$$\mathrm{RERI} = \mathrm{RR}_{ab} - \mathrm{RR}_a - \mathrm{RR}_b + 1$$
$$\mathrm{AP} = (\mathrm{RR}_{ab} - \mathrm{RR}_a - \mathrm{RR}_b + 1)/\mathrm{RR}_{ab} = \mathrm{RERI}/\mathrm{RR}_{ab}$$
$$\mathrm{SI} = (\mathrm{RR}_{ab} - 1)/\left((\mathrm{RR}_a - 1) + (\mathrm{RR}_b - 1)\right)$$

where RR*ab* represents the relative risk (RR) in the group exposed to factors both *a* and *b* compared to the group that was not exposed to either factor.

An RERI or AP value of 0 indicates no additive interaction, whereas ≥0 suggests a positive interaction. A statistically significant interaction was defined as one where the 95% confidence interval (CI) of SI did not include 1, and the 95% CI of RERI or AP did not include 0.[17] Additionally, we examined the effect modification of physical activity (physically active versus physically inactive) between myopia and T2DM by assessing the multiplicative interaction with RR and 95% CI.[17] Physical activity levels were assessed using the revised International Physical Activity Questionnaire, which includes the frequency and duration of walking, moderate, and vigorous activity (field's ID 864, 874, 884, 894, 904, and 914). Physical activity levels were defined as physically active if moderate-to-vigorous physical activity exceeded 150 minutes per week[18]; otherwise, they were classified as physically inactive.

All statistical analyses were conducted using R version 4.3.2, and statistical significance was defined as a two-sided *P* value < 0.05.

Results

Study Population

The participants' demographics are presented in Table 1. This study comprised 116,245 participants with available refractometry and blood biochemistry test results from the UKB. The mean age was 57.1 years, with 54% being women and predominantly Caucasian (90.8%). Approximately 35% had attained a high level of education. The average BMI was 27.4, with 11,208 (9.6%) classified as current smokers and 50,050 (43.1%) as frequent alcohol drinkers. At baseline, 32,639 (28.1%) participants had hypertension, and 6837

Table 1. Baseline Characteristics of Study Participants by Sex

Participant Characteristics	All Participants (*n* = 116,245)	Female Participants (*n* = 62,819)	Male Participants (*n* = 53,426)
Age, mean (SD), y	57.1 (7.98)	56.7 (7.96)	57.6 (7.98)
Ethnicity, *n* (%)			
White	105,523 (90.8)	56,776 (90.4)	48,747 (91.2)
Others	10,722 (9.22)	6,043 (9.62)	4,679 (8.76)
Education level, *n* (%)			
Low	75,579 (65.0)	41,425 (65.9)	34,154 (63.9)
High	40,666 (35.0)	21,394 (34.1)	19,272 (36.1)
Townsend deprivation index fifth, *n* (%)			
First (least deprived)	23,091 (19.9)	12,242 (19.5)	10,849 (20.3)
Second	23,201 (20.0)	12,467 (19.8)	10,734 (20.1)
Third	23,200 (20.0)	12,586 (20.0)	10,614 (19.9)
Fourth	23,208 (20.0)	12,938 (20.6)	10,270 (19.2)
Fifth (most deprived)	23,545 (20.3)	12,586 (20.0)	10,959 (20.5)
BMI, mean (SD), *kg/m^2*	27.4 (4.80)	27.1 (5.21)	27.8 (4.23)
Alcohol intake, *n* (%)			
Never or seldom	22,957 (19.7)	14,601 (23.2)	8,356 (15.6)
Moderate	43,238 (37.2)	25,532 (40.6)	17,706 (33.1)
Frequent	50,050 (43.1)	22,686 (36.1)	27,364 (51.2)
Smoking status, *n* (%)			
Never	64,170 (55.2)	37,890 (60.3)	26,280 (49.2)
Previous	40,867 (35.2)	19,885 (31.7)	20,982 (39.3)
Current	11,208 (9.64)	5,044 (8.03)	6,164 (11.5)
Hypertension history, *n* (%)			
No	83,606 (71.9)	47,970 (76.4)	35,636 (66.7)
Yes	32,639 (28.1)	14,849 (23.6)	17,790 (33.3)
Diabetes history, *n* (%)			
No	109,408 (94.1)	60,129 (95.7)	49,279 (92.2)
Yes	6,837 (5.88)	2,690 (4.28)	4,147 (7.76)
SE, mean (SD), Diopter	−0.20 (2.41)	−0.20 (2.45)	−0.20 (2.37)
Myopia diagnosis, *n* (%)			
No	81,780 (70.4)	44,217 (70.4)	37,563 (70.3)
Yes	34,465 (29.6)	18,602 (29.6)	15,863 (29.7)

Values are mean (standard deviation) or numbers (percentage).
BMI, body mass index; SD, standard deviation; SE, spherical equivalent.

Investigative Ophthalmology & Visual Science

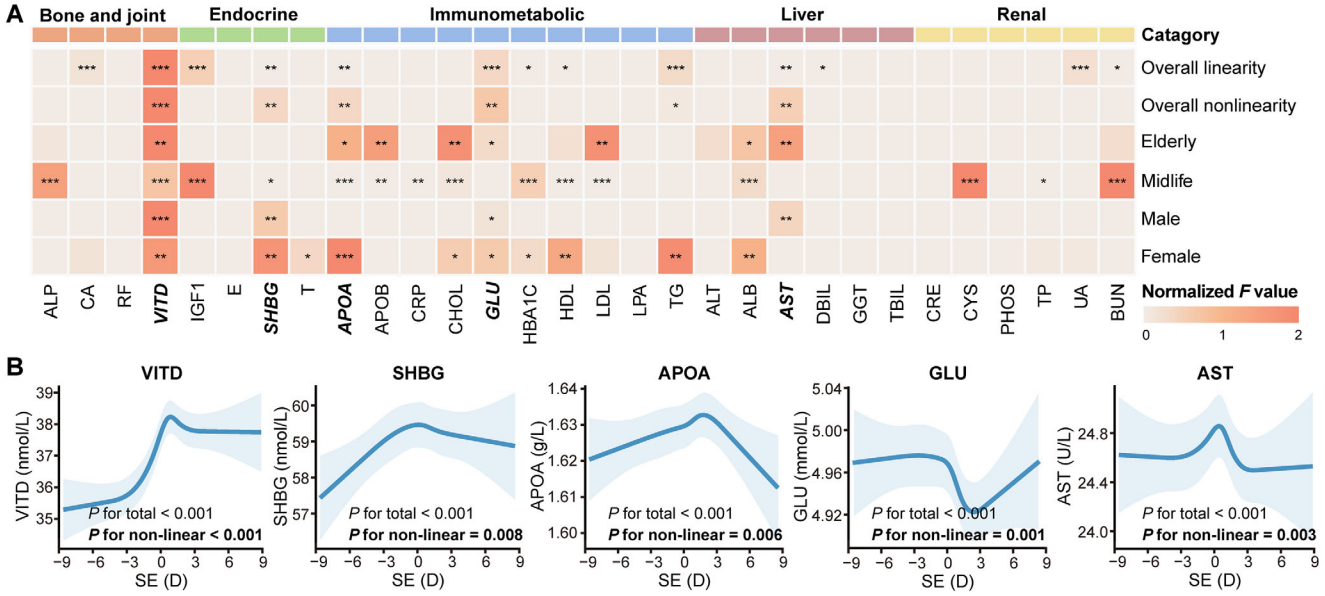

Figure 2. Associations of SE with blood biochemistry tests. (**A**) Heatmap overview the results of restricted cubic spline models (linearity and nonlinearity associations) and sensitivity analysis (restricted cubic spline models in midlife, elderly, and female and male participants, respectively). The color represents normalized *F* value. **P* < 0.05, ***P* < 0.01, ****P* < 0.001. (**B**) Restricted cubic spline models fitted for linear model estimation using ordinary least squares to overview the associations among SE and vitamin D, SHBG, APOA, glucose, and AST. ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APOA, apolipoprotein A; APOB, apolipoprotein B; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CA, calcium; CHOL, cholesterol; CRE, creatinine; CRP, C-reactive protein; CYS, cysteine; DBIL, direct bilirubin; E, estrogen; GGT, gamma-glutamyl transferase; GLU, glucose; HBA1C, hemoglobin A1c; HDL, high-density lipoprotein; IGF1, insulin-like growth factor 1; LDL, low-density lipoprotein; LPA, lipoprotein (A); PHOS, phosphate; RF, rheumatoid factor; SHBG, sex hormone-binding globulin; T, testosterone; TBIL, total bilirubin; TG, triglycerides; TP, total protein; SE, spherical equivalent; UA, urate; VITD, vitamin D.

(5.9%) had diabetes. The mean SE for all participants was −0.20 D, with 34,465 (29.6%) categorized as having myopia.

Associations Between SE and Blood Biochemistry Parameters

To explore the relationship between refractive error and common chronic disease risk, we analyzed the association between SE and key blood biochemical parameters. Figure 2A presents the results of the RCS models, illustrating both linear and nonlinear associations, along with stratum analysis for age and sex (for detailed results, refer to Supplementary Table S3). Among the 30 parameters across 5 categories, SE was primarily associated with vitamin D, sex hormone binding globulin (SHBG), apolipoprotein A (APOA), blood glucose, and aspartate aminotransferase (AST), all significantly associated in at least 4 analyses. To test the nature of the association of SE with these five blood biochemical tests, we visualized the results of the RCS model and stratified analyses in Figure 2B and Supplementary Figure S1, and the results were generally consistent. After fully adjusting for covariates, the RCS model demonstrated that vitamin D levels increased nonlinearly with SE, showing a steeper rise around plano. SHBG and APOA levels displayed nonlinear relationships, with a slight increase in myopia status and a decrease in hyperopia status. Blood glucose levels remained stable for myopia status but decreased sharply around plano, and then slightly increased in the moderate-to-high hyperopia status. Last, AST levels increased and then slightly decreased around plano. These findings underscore the complexity of the relationships between refractive status and systemic biochemical markers, emphasizing the need to consider nonlinear dynamics in epidemiological research.

Associations Between SE and Common Chronic Diseases

Building on the observed correlation between SE and blood biochemical parameters, we investigated the relationship between SE and osteoporosis (related to vitamin D and SHBG), hyperlipidemia (related to APOA), T2DM (related to blood glucose), and chronic liver disease (related to AST). The results of the RCS and CPH modeling are presented in Figure 3, revealing that only T2DM incidence exhibited a significant nonlinear relationship with SE (*P* for nonlinearity = 0.021) throughout a median follow-up period of 9.12 years. Notably, we observed a reverse S-shaped association between SE and the risk of incident T2DM. Moreover, within the myopia interval, the hazard ratio (HR) and 95% CI for T2DM risk were significantly greater than one, suggesting that individuals with myopia may face an elevated risk of developing T2DM compared to those without myopia.

Sensitivity Analysis of the Association Among SE, Myopia, and T2DM

The sensitivity analysis aimed to assess the robustness and reliability of the observed associations among SE, myopia, and T2DM. We categorized SE into five levels relative to the average SE. Individuals with the lowest 5% SE (indicating

Investigative Ophthalmology & Visual Science

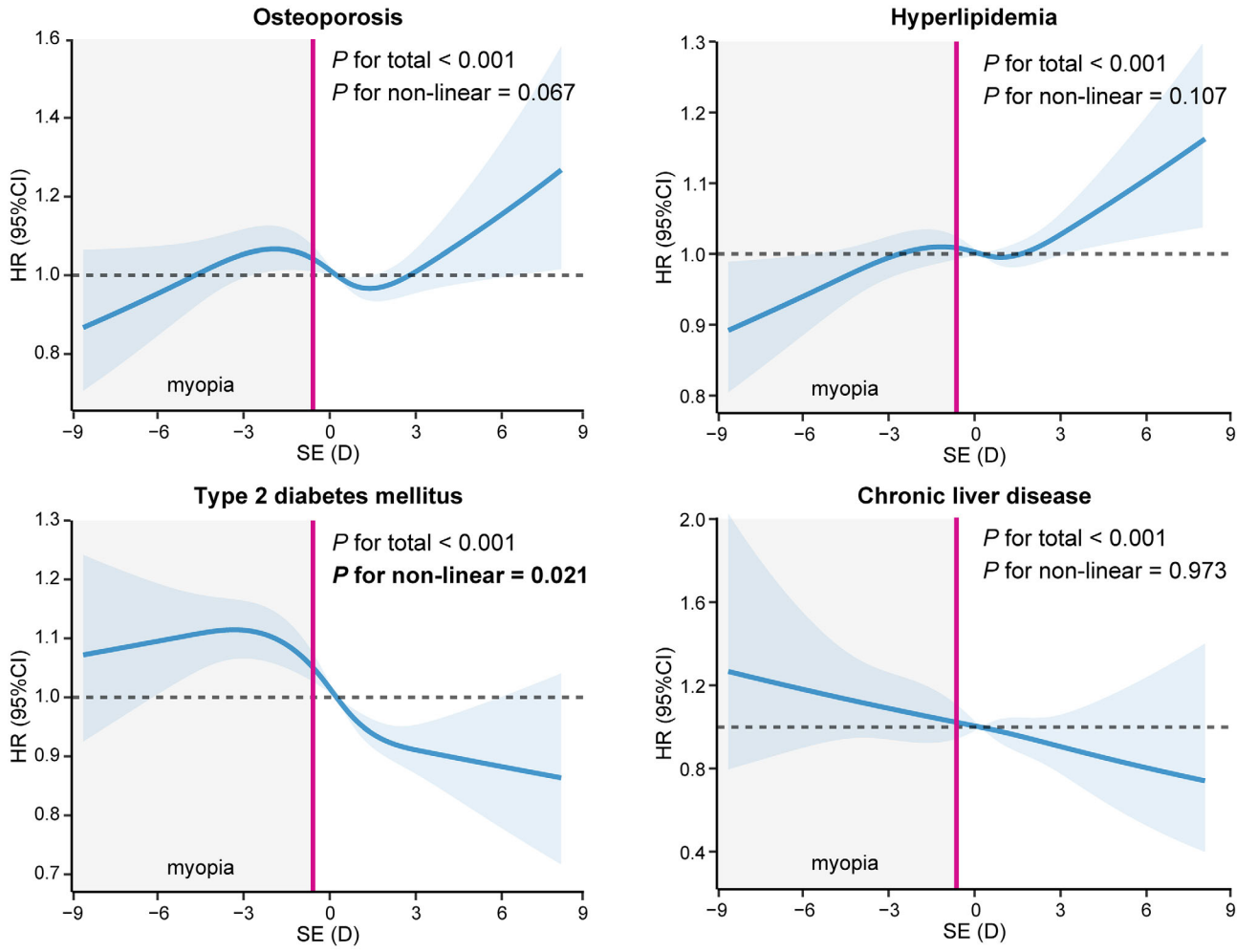

Figure 3. Nonlinear associations between SE and disease indicated by blood biochemistry tests. Restricted cubic spline models fitted for Cox proportional hazards models with five knots. The *pink vertical line* represents −0.75 D which is the criteria of myopia. Results were adjusted for age, sex, ethnicity, education level, Townsend deprivation index, BMI, smoking status, alcohol drink status, and hypertension. CI, confidence interval; D, diopter; HR, hazard ratio; SE, spherical equivalent.

the most myopia) and those with SE in the lowest 5% to 25% range had a 12% (adjusted HR = 1.12, 95% CI = 1.01–1.25, $P = 0.004$) and 9% (adjusted HR = 1.09, 95% CI = 1.03–1.15, $P = 0.029$) higher T2DM risk, respectively. Conversely, individuals in the highest 5% to 25% and highest 5% SE ranges (indicating the most hyperopia) had a decreased risk, with adjusted HRs of 0.92 (95% CI = 0.88–0.98, $P = 0.008$) and 0.89 (95% CI = 0.81–0.98, $P = 0.024$), respectively. Additionally, each diopter shift toward hyperopia was associated with a 3% lower risk of T2DM incidence (adjusted HR = 0.97, 95% CI = 0.97–0.98, $P < 0.001$). Compared to those without myopia, individuals with myopia showed a 13% (adjusted HR = 1.13, 95% CI = 1.08–1.19, $P = 0.001$) higher risk of T2DM incidence (Table 2).

In the stratum-specific analysis based on age, sex, and follow-up time, significant associations between SE and T2DM incidence were found, except in elderly individuals (P for nonlinearity = 0.639) and those with less than 5 years of follow-up (P for nonlinearity = 0.288; Supplementary Fig. S2). Moreover, HRs consistently indicated a range of 11% to 15% higher risk of T2DM incidence in individuals with myopia compared to those without myopia across different age, sex, and follow-up time categories (all $P \leq 0.005$; Supplementary Tables S4–S9).

Effect of Additive Interaction and Modification

An interaction analysis was conducted to explore potential interactions between myopia and obesity and their combined effects on T2DM incidence (Table 3). The measure of interaction on a multiplicative scale, indicated by the ratio of HRs, was 1.14 (95% CI = 1.04–1.25, $P = 0.007$). This indicates a substantial joint effect of obesity and myopia together on the HR scale, surpassing the product of their individual effects. Furthermore, there were indications of a positive interaction effect on the additive scale when considering obesity and myopia together, which exceeds the combined effects of obesity alone and myopia alone, with an RERI of 0.52 (95% CI = 0.30–0.74). These results suggested that when myopia and obesity coexisted, the interaction effect of myopia and obesity was 1.28 times (95% CI = 1.15–1.42) the sum of the effects of the two alone. The AP was 0.15 (95% CI = 0.09–0.21), indicating that 15% of the combined risk of myopia and obesity was due to the interaction.

Table 2. SE and Myopia in Relation to T2DM Risk

Characteristics	No. of Events (%)	Model I		Model II	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
SE at baseline*					
Lowest 5%	439 (7.7)	1.11 (1.03–1.23)	0.003	1.12 (1.01–1.25)	0.004
Lowest 5% to 25%	1870 (8.2)	1.08 (1.02–1.14)	0.008	1.09 (1.03–1.15)	0.029
Around average	4180 (7.4)	1.00		1.00	
Highest 5% to 25%	1650 (7.2)	0.93 (0.88–0.98)	0.009	0.92 (0.88–0.98)	0.008
Highest 5%	386 (6.8)	0.91 (0.82–0.98)	0.031	0.89 (0.81–0.98)	0.024
Pre 1 diopter hyperopia shift		0.97 (0.96–0.98)	<0.001	0.97 (0.97–0.98)	<0.001
Myopia, yes *vs* no	2386 (7.6) vs. 6089 (7.2)	1.12 (1.07–1.18)	<0.001	1.13 (1.08–1.19)	<0.001

BMI, body mass index; CI, confidential interval; HR, hazard ratio; SE, spherical equivalent; T2DM, type 2 diabetes mellitus.

Model I: Adjusted for age, sex, ethnicity, education level, Townsend deprivation index, and BMI. Model II: model I with additional adjustment for smoking status alcohol drink status, and hypertension.

* The critical values for the lowest 5%, lowest 25%, highest 25%, and highest 5% SE values are −5.03 D, −1.14 D, 1.11 D, and 3.23 D, respectively.

Table 3. Interaction Between Myopia and BMI on the Risk of T2DM

	Non-Myopia	Myopia	Effect of Myopia Within the Strata of Obesity
Non-obesity	1 (Reference)	1.06 (0.99–1.13)	1.06 (0.99–1.13)
		$P = 0.109$	$P = 0.109$
Obesity*	2.82 (2.67–2.96)	3.39 (3.17–3.63)	1.20 (1.13–1.29)
	$P < 0.001$	$P < 0.001$	$P < 0.001$
Effect of obesity within the strata of myopia	2.82 (2.67–2.96)	3.21 (2.96–3.48)	
	$P < 0.001$	$P < 0.001$	
Additive scale	1.14 (1.04–1.25)		
	$P = 0.007$		
RERI	0.52 (0.30–0.74)		
AP	0.15 (0.09–0.21)		
SI	1.28 (1.15–1.42)		

AP, attributable proportion due to interaction; BMI, body mass index; HR, hazard ratio; RERI, relative excess risk due to interaction; SI, synergy index; T2DM, type 2 diabetes mellitus.

HR is adjusted for age, sex, ethnicity, education level, Townsend deprivation index, smoking status, alcohol drink status, and hypertension.

* Obesity is defined as BMI $\geq$ 30 kg/m^2.

Additionally, the effects of modifications, particularly regarding physical activity levels, were investigated to understand how physical activity may modify the relationship between myopia and T2DM incidence (Supplementary Table S10). Comparing participants without myopia who were physically active, the risk of T2DM incidence was not significantly elevated for participants with myopia who were physically active (adjusted HR = 1.06, 95% CI = 0.93–1.20, $P = 0.353$), nor for those who were physically inactive without myopia (adjusted HR = 0.96, 95% CI = 0.88–1.05, $P = 0.400$). However, when myopia and physical inactivity were combined, there was a 23% increase in the risk of T2DM incidence (adjusted HR = 1.23, 95% CI = 1.11–1.36, $P < 0.001$). These HRs indicated that the risk of T2DM for patients with myopia is evident only in the physically inactive group.

Discussion

In this large prospective cohort study, our findings unveiled multiple connections between SE and markers indicative of specific dysfunctions, such as mineral and bone metabolism (vitamin D and SHBG), lipid dysregulation (APOA), blood glucose, and liver abnormalities (AST). Additionally, we confirmed that myopia contributes to an 11% to 15% higher risk of developing T2DM. Furthermore, we identified that obesity mediates the contribution of myopia to T2DM incidence, and engaging in adequate physical activity can mitigate the increased risk associated with myopia. To the best of our knowledge, this is the first comprehensive prospective study on a large scale to systematically investigate the relationship between refractive errors and common chronic diseases.

Maintaining internal homeostasis is a complex process involving nearly all organs. Whereas the eye is an important sense organ, its diseases are now recognized as causes of chronic diseases rather than direct indicators.[19] In Ma et al.'s study, cataracts showed an HR of 1.21 for all-cause dementia risk.[3] Shang et al. found age-related macular degeneration and diabetes-related eye disease associated with HRs of 1.26 and 1.61 for all-cause dementia risk, respectively.[5] Fundus changes correlated with Parkinson's and kidney disease.[4,7] Additionally, intraocular pressure and glaucoma are linked to cardiovascular disease.[2,6,8] However, refractive errors, the main cause of vision impairment often persisting from early life, have not been fully understood in terms of their health impact on common chronic disease development.[10,12]

In our analysis, we investigated the association between refractive errors and blood biochemistry, examining the correlation between SE and these metrics. Overall, linear associations predominated over nonlinear ones, particularly in women and midlife participants compared to men and

the elderly. We hypothesized that the impact of refractive errors might differ between myopia and hyperopia, as indicated by the prevalence of linear associations. Furthermore, this impact seemed more pronounced in women and may decrease with age. Given that refractive errors stem from a blend of genetic and environmental influences,[20,21] we suggest that lifestyle risk factors associated with refractive errors persist into adulthood. However, these factors may overlap with those causing certain diseases in men and the elderly, potentially weakening the influence of lifestyle behind the "refractive error" phenotype.

Next, we examined common chronic diseases associated with significant blood markers to validate associations with refractive errors. We found no significant association among SE and osteoporosis, hyperlipidemia, or chronic liver disease. This suggests that although refractive errors may influence certain indicators, they do not impact the overall occurrence of these three diseases. However, we observed a reverse S-shaped association between SE and T2DM incidence. This led us to focus on the association between myopia and T2DM incidence, as the HR and 95% CI exceeded the HR = 1 reference line in the myopic interval. Despite no significant nonlinear associations between SE and T2DM incidence in the elderly or those with less than years of follow-up, we still observed a robust 11% to 15% higher risk of T2DM incidence among participants with myopia compared to those without myopia. Considering the temporal sequence of myopia development and T2DM, we concluded that susceptibility to T2DM is higher in the myopic group, establishing myopia as a new independent risk factor for T2DM.

In a cross-sectional study that included 1414 Indian patients with diabetes over 40 years old, researchers observed a refractive error prevalence of 60%, surpassing the average prevalence of refractive error in India.[22] Although this study demonstrated that refractive error in patients with diabetes was relatively high, our study provides complementary evidence that people with myopia may be more likely to develop diabetes. In a retrospective cohort study spanning nearly 20 years and involving over 1 million adolescents aged 16 to 19 years in Israel, myopia was linked to early-onset T2DM among female patients.[23] Combining these findings with ours, we suggest that there is a cumulative effect of myopia on T2DM, possibly with sex-specific differences in accumulation rates.

Several potential mechanisms have been put forward explaining the relationship between myopia and T2DM. It is well-established that the insulin and insulin-like growth factor-1 (IGF-1) signaling pathway is crucial for maintaining β-cells' function, whereas disruptions in this pathway could lead to insulin resistance, hyperinsulinemia, and eventually the development of T2DM.[24,25] In addition, increased insulin and IGF-1 could contribute to the axial length elongation by stimulating differentiation and cell proliferation.[26,27] Similar to IGF-1, the expression of retinal insulin-like growth factor-2 (IGF-2) was significantly upregulated in form-deprivation myopic guinea pig and correlated with myopia development and eye growth.[28,29] Consequently, myopia and T2DM might share a common pathophysiological pathway mediated by insulin resistance.[30] Further studies are warranted to understand how myopia contributes to a higher risk of developing T2DM.

To explore potential lifestyle associations between myopia and the incidence of T2DM and to provide preventive strategies, we focused on modifiable lifestyle factors, given the significant lifestyle-related risk factors associated with both conditions.[20,31] Obesity, a known risk factor and comorbidity of myopia in both children and adults is also a well-established risk factor for T2DM.[23,32–34] Therefore, we conducted additive interaction analyses to explore whether there is an excess risk of interaction between myopia and obesity status in T2DM incidence. Our results support the presence of such an interaction, indicating that patients with myopia and obesity face a higher risk of T2DM onset than the combined risk of myopia and obesity alone. Additionally, we conducted an effect modification analysis to identify preventive measures, such as physical activity.[35] Our findings revealed that the risk of myopia leading to T2DM was evident only in the physically inactive population, suggesting that active participation in physical activity could protect against T2DM incidence among individuals with myopia.

Our study's strengths lie in using longitudinal analyses to assess the association between refractive errors and common chronic diseases as opposed to cross-sectional methods. Furthermore, we leveraged a large sample size, an extensive follow-up duration, and a comprehensive consideration of covariates and diagnoses derived from hospital inpatient records.

However, several limitations warrant acknowledgment. First, as UKB participants are predominantly European, younger, healthier, and more educated, generalizability to other populations requires further validation.[36] Second, unaccounted-for covariates are possible, and the reliability of included covariates, particularly self-reported measures like alcohol and smoking status, may be limited. Third, given the observational nature of our study, we are unable to establish any cause-effect relationships. Fourth, due to the exploratory nature of our study, we did not apply stringent corrections for multiple comparisons, which may increase the risk of type I errors. This approach, while aimed at uncovering potential associations between spherical equivalent and various blood biochemical indicators, necessitates validation in future studies. Last, our selection of 30 available blood markers may not encompass all relevant parameters, potentially overlooking important indicators or other diseases. Future studies could explore the underlying biological mechanisms between myopia and the development of T2DM and investigate the effectiveness of targeted interventions, such as lifestyle modification and weight control, in reducing the risk of T2DM in patients with myopia.

In conclusion, our study identified significant associations between SE and markers, including vitamin D, SHBG, APOA, blood glucose, and AST within a large population-based cohort. Furthermore, we discovered that myopia is associated with a 13% higher risk of T2DM, highlighting it as a novel risk factor for T2DM. Our study also emphasizes the importance of weight control and physical activity to prevent T2DM among individuals with myopia, highlighting that the benefits of physical activity are particularly significant for this group. Importantly, our study contributes to a broader understanding of how refractive errors impact overall health, particularly in primary care settings for middle-aged and elderly individuals.

Acknowledgments

The present study was conducted using the UK Biobank resource under the application number 105765. The authros

are grateful to all the participants and researchers from the UK Biobank.

Supported by the National Natural Science Foundation of China (Grant Nos. 82271119 and 82304260); Shanghai Rising-Star Program (Grant No. 23QA1401000); China Postdoctoral Science Foundation (Grant No. 2023M730626); Healthy Young Talents Project of Shanghai Municipal Health Commission (Grant No. 2022YQ015); and Project of Shanghai Science and Technology (Grant Nos. 20410710100 and 21Y11909800).

Author Contributions: Y.J., X.Z., and J.Z. conceived and designed the study. Y.Yu, H.C., and Z.W. performed the statistical analyses. Y.Yu and H.C. wrote the first draft of the manuscript. Y.Yu, Z.Z., Y.Ye, and Y.B. acquired and interpreted the data. All authors contributed to the interpretation of the results and critical revision of the manuscript. All authors approved the final version of the manuscript. J.Z. is the guarantor of this work and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data Availability: All data relevant to the study were acquired from the UK Biobank Resource under application number 105765. Data can be accessed through applications on UK Biobank website (https://www.ukbiobank.ac.uk/).

Ethics Approval: Ethical approval was obtained from the National Health Service National Research Ethics Service (Ref: 11/NW/0382). All participants provided electronic informed consent.

Disclosure: **Y. Yu**, None; **H. Chen**, None; **Z. Wang**, None; **Y. Ye**, None; **Z. Zhang**, None; **Y. Bao**, None; **Y. Jia**, None; **X. Zhou**, None; **J. Zhao**, None

References

1. Cumberland PM, Rahi JS. Visual function, social position, and health and life chances: the UK Biobank Study. *JAMA Ophthalmol*. 2016;134(9):959–966.
2. Wang Y, Liang Y, Seth I, et al. Determinants of incident atherosclerotic cardiovascular disease events and all-cause mortality in patients with age-related macular degeneration: prospective cohort study of UK Biobank. *Asia Pac J Ophthalmol (Phila)*. 2023;12(3):293–302.
3. Ma LZ, Zhang YR, Li YZ, et al. Cataract, cataract surgery, and risk of incident dementia: a prospective cohort study of 300,823 participants. *Biol Psychiatry*. 2023;93(9):810–819.
4. Paterson EN, Cardwell C, MacGillivray TJ, et al. Investigation of associations between retinal microvascular parameters and albuminuria in UK Biobank: a cross-sectional case-control study. *BMC Nephrol*. 2021;22(1):72.
5. Shang X, Zhu Z, Huang Y, et al. Associations of ophthalmic and systemic conditions with incident dementia in the UK Biobank. *Br J Ophthalmol*. 2023;107(2):275–282.
6. Ye S, Chang Y, Kim CW, et al. Intraocular pressure and coronary artery calcification in asymptomatic men and women. *Br J Ophthalmol*. 2015;99(7):932–936.
7. Wagner SK, Romero-Bascones D, Cortina-Borja M, et al. Retinal optical coherence tomography features associated with incident and prevalent Parkinson disease. *Neurology*. 2023;101(16):e1581–e1593.
8. Choi JA, Lee SN, Jung SH, Won HH, Yun JS. Association of glaucoma and lifestyle with incident cardiovascular disease: a longitudinal prospective study from UK Biobank. *Sci Rep*. 2023;13(1):2712.
9. World Health Organization (WHO). World report on vision. 2019. Available at: https://www.who.int/publications/i/item/9789241516570.
10. GBD 2019 Blindness and Vision Impairment Collaborators; Vision Loss Expert Group of the Global Burden of Disease Study. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. *Lancet Glob Health*. 2021;9(2):e144–e160.
11. Xu T, Wang B, Liu H, et al. Prevalence and causes of vision loss in China from 1990 to 2019: findings from the Global Burden of Disease Study 2019. *Lancet Public Health*. 2020;5(12):e682–e691.
12. Iribarren R. Crystalline lens and refractive development. *Prog Retin Eye Res*. 2015;47:86–106.
13. Foster PJ, Atan D, Khawaja A, et al. Cohort profile: rationale and methods of UK Biobank repeat imaging study eye measures to study dementia. *BMJ Open*. 2023;13(6):e069258.
14. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Medicine*. 2015;12(3):e1001779.
15. Philippe P, Mansi O. Nonlinearity in the epidemiology of complex health and disease processes. *Theor Med Bioeth*. 1998;19(6):591–607.
16. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. 3rd edition. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
17. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. *Int J Epidemiol*. 2012;41(2):514–520.
18. WHO Guidelines Approved by the Guidelines Review Committee. *Global Recommendations on Physical Activity for Health*. World Health Organization Copyright © World Health Organization 2010. 2010. Available at: https://www.who.int/docs/default-source/physical-activity/information-sheet-global-recommendations-on-physical-activity-for-health/physical-activity-recommendations-18-64years.pdf#:~:text=Adults%20aged%2018%E2%80%9364%20should%20do%20at%20least%20150,equivalent%20combination%20of%20moderate%20-%20and%20vigorous-intensity%20activity.
19. Wu JH, Duan CH, Yang YF, et al. Insights into the liver-eyes connections, from epidemiological, mechanical studies to clinical translation. *J Transl Med*. 2023;21(1):712.
20. Enthoven CA, Tideman JWL, Polling JR, et al. Interaction between lifestyle and genetic susceptibility in myopia: the Generation R study. *Eur J Epidemiol*. 2019;34(8):777–784.
21. Rahi JS, Cumberland PM, Peckham CS. Myopia over the lifecourse: prevalence and early life influences in the 1958 British birth cohort. *Ophthalmology*. 2011;118(5):797–804.
22. Rani PK, Raman R, Rachapalli SR, Kulothungan V, Kumaramanickavel G, Sharma T. Prevalence of refractive errors and associated risk factors in subjects with type 2 diabetes mellitus. *Ophthalmology*. 2010;117(6):1155–1162.
23. Peled A, Raz I, Zucker I, et al. Myopia and early-onset type 2 diabetes: a nationwide cohort study. *J Clin Endocr Metab*. 2022;107(2):E663–E671.
24. Batista TM, Haider N, Kahn CR. Defining the underlying defect in insulin action in type 2 diabetes. *Diabetologia*. 2021;64(5):994–1006.
25. Rachdaoui N. Insulin: the friend and the foe in the development of type 2 diabetes mellitus. *Int J Mol Sci*. 2020;21(5):1770.
26. Feldkaemper MP, Neacsu I, Schaeffel F. Insulin acts as a powerful stimulator of axial myopia in chicks. *Invest Ophthalmol Vis Sci*. 2009;50(1):13–23.
27. Liu X, Wang P, Qu C, et al. Genetic association study between insulin pathway related genes and high myopia in a Han Chinese population. *Mol Biol Rep*. 2015;42(1):303–310.

28. Deng ZH, Tan J, Liu SZ, Zhao SZ, Wang JT. The correlation between the regulation of recombinant human IGF-2 on eye growth and form-deprivation in guinea pig. *Graefes Arch Clin Exp Ophthalmol*. 2010;248(4):519–525.
29. Tang RH, Tan J, Deng ZH, Zhao SZ, Miao YB, Zhang WJ. Insulin-like growth factor-2 antisense oligonucleotides inhibits myopia by expression blocking of retinal insulin-like growth factor-2 in guinea pig. *Clin Exp Ophthalmol*. 2012;40(5):503–511.
30. Galvis V, López-Jaramillo P, Tello A, et al. Is myopia another clinical manifestation of insulin resistance? *Med Hypotheses*. 2016;90:32–40.
31. Zhang YB, Pan XF, Chen JX, et al. Combined lifestyle factors and risk of incident type 2 diabetes and prognosis among individuals with type 2 diabetes: a systematic review and meta-analysis of prospective cohort studies. *Diabetologia*. 2020;63(1):21–33.
32. Harrington SC, Stack J, O'Dwyer V. Risk factors associated with myopia in schoolchildren in Ireland. *Br J Ophthalmol*. 2019;103(12):1803–1809.
33. Peled A, Nitzan I, Megreli J, et al. Myopia and BMI: a nationwide study of 1.3 million adolescents. *Obesity (Silver Spring)*. 2022;30(8):1691–1698.
34. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. *Lancet*. 2017;389(10085):2239–2251.
35. Boulé NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA*. 2001;286(10):1218–1227.
36. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol*. 2017;186(9):1026–1034.

Investigative Ophthalmology & Visual Science