Associations Between a Healthy Lifestyle Score and Retinal Neurovascular Health

Sub-title: Lifestyle Score and Retinal Neurovascular Health

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Synopsis: A higher healthy lifestyle score was associated with better retinal neurovascular health and reduced major retinal diseases in a dose-response manner.

ABSTRACT

Aims: To investigate the associations between a healthy lifestyle score and retinal neurovascular health, and to explore whether lower inflammation levels mediate these associations.

Methods: This study based on UK Biobank. The healthy lifestyle scores ranged from 0 to 6 and comprised physical activity, diet, sleep duration, smoking status, alcohol consumption, and body weight. Outcomes included retinal diseases [age-related macular degeneration (AMD) and retinal vascular occlusion (RVO)] from hospital admission records (378,649 participants), retinal vascular metrics from retinal photography (32,226 participants), and retinal neural metrics from optical coherence tomography (42,557 participants). An INFLA-score was used to characterize inflammation levels.

Results: Participants with better healthy life score (scored from 5 to 6) were associated with a 29% lower risk of AMD, 25% lower risk of RVO, 2% increase in artery-to-vein ratio (AVRE), 0.22um increase in central retinal vein equivalent (CRVE), 0.36um decrease in central retinal artery equivalent(CRAE), 0.004 increase in FD, 0.38um increase in retinal nerve fiber layer, 0.69um increase in ganglion cell-inner plexiform layer (GCIPL), and 0.35um increase in photoreceptor segment(PS) compared with those with worst lifestyle score (scored from 0 to 1) (all p_{trend} <0.01). In addition, INFLA-score partially mediate the associations between healthy lifestyle scores and increased risk of AMD [mediated proportion(MP): 14.8%], higher AVRE(MP:12.76%), narrower CRVE(MP:24.49%), thicker GCIPL(MP:4.97%), and thicker PS (MP:26.86%).

Conclusion: Great adherence to a healthier lifestyle was associated with better retinal health in a dose-response manner. Lower inflammation partially mediated the associations between healthy lifestyle scores and retinal health.

Keywords: healthy lifestyle behaviors, retinal neurovascular health, inflammation, UK biobank

Key messages

What is already known on this topic - summarise the state of scientific knowledge on this subject before you did your study and why this study needed to be done

Maintaining retinal neurovascular health is crucial not only for preserving sight but also for providing insights of the overall well-being. Lifestyle behaviors are important modifiable risk factors for retinal health. Nevertheless, the associations between combined healthy lifestyle behaviors and retinal health remains to be quantified.

What this study adds - summarise what we now know as a result of this study that we did not know before

A higher healthy lifestyle score was associated with better retinal neurovascular health and reduce the risk of corresponding retinal diseases in a dose-response manner. Lower inflammation partially mediated the associations between healthy lifestyle scores and retinal health.

How this study might affect research, practice or policy - summarise the implications of this study

By prioritizing preventive care through lifestyle adjustments, individuals can potentially delay the onset and progression of retinal diseases and diminish the need for extensive long-term care.

1. Introduction

Retinal health is a critical aspect of eye care that extends beyond vision alone. Adverse factors can accelerate retinal neurodegeneration and vascular abnormal changes, which may increase the subsequent risk of retinal diseases such as age-related macular degeneration (AMD) and retinal vascular disease (RVO), leading to vision loss and blindness[1]. Furthermore, maintaining retinal health is crucial not only for preserving sight but also for providing insights of the overall well-being. Imaging of the retina may be used to reflect pathological changes of the circulatory and central nervous systems. For example, retinal vascular alterations, such as arterial narrowing and venous dilation have been observed to be associated with future risk of cardiovascular diseases (CVD)[2]. Thinner photoreceptor segment (PS) layers were associated with a higher risk of mortality and various chronic diseases[3]. Additionally, retinal diseases have been shown associated with an increased risk of neurodegenerative diseases and CVD[4,5]. Therefore, identifying effective strategies to maintain retinal health is of paramount importance, not only for maintaining visual health but also for overall health.

Lifestyle behaviors are significant modifiable risk factors for retinal neurovascular health. For instance, smoking is widely recognized as a major non-genetic risk factor for AMD, and smoking cessation has been shown to effectively reduce the risk of developing AMD[6]. Higher levels of physical activity was associated with slower rates of macular ganglion cell-inner plexiform layer (GCIPL) thinning in the PROGRESSA study[7],and were also associated with narrower venular calibers and a wider central retinal arteriolar equivalent (CRAE)[8]. Moreover, sleep disorders can adversely affect retinal structure and function, emphasizing the importance of maintaining a healthy sleep pattern for preserving retinal health[9]. However, while previous studies have primarily focused on the impact of single lifestyle behavior on the retina, and the combined healthy lifestyle factors and retinal neurovascular health remain insufficiently explored.

Furthermore, it is important to consider how lifestyle behaviors influence retinal health, as this might enhance understanding of mechanisms that improve retinal health and support more targeted interventions for at-risk individuals. Chronic inflammation is implicated in various retinal vascular diseases[10], where elevated levels of inflammatory markers can contribute to retinal cell dysfunction, blood retinal barrier disruption, and neovascularization[11]. Previous research has shown that healthy lifestyle behaviors significantly lower inflammatory biomarker levels[15]. However, the extent to which inflammatory biomarkers may mediate the relationship between lifestyle scores and retinal metrics remains largely unclear.

To fill the knowledge gap, we examined the associations between a healthy lifestyle score and retinal neurovascular health using data from the UK Biobank cohort. Additionally, we evaluated the mediating role of inflammatory levels in these associations

2. Methods

2.1. Study Population

The UK Biobank consists of approximately 500,000 participants aged 40 to 73 years registered with the National Health Service in the UK. Participants were assessed at baseline between 2006 and 2010 and attended one of the 22 assessment centres throughout the UK where they provided information on geographic factors, lifestyle, and other health-related aspects through comprehensive baseline questionnaires, interviews, and physical measurements[12]. This study comprised three samples based on the outcomes: 378,648 participants in the retinal disease samples, 32,226 participants in the retinal vascular metric samples, and 42,557 participants in the retinal neural metric samples. Detailed inclusion and exclusion criteria for these samples are shown in **sFigure 1**. Data used in the present study was accessed through the Biobank Consortium (Application No: 86091). This study was carried out in accordance with the Helsinki declaration, and informed consent was provided from all participants.

2.2. Exposure Ascertainment

Healthy lifestyle scores were constructed based on six lifestyle behaviors (physical activity, diet, sleep duration, smoking status, alcohol consumption, and body weight). The definitions of these behaviors are presented in the **sMethods**. Participants scored 1 point for each of the 6 healthy behaviors. The healthy lifestyle scores ranged from 0 to 6, with higher scores indicating higher adherence to a healthy lifestyle. Due to the relatively smaller sample sizes for scores 0, 1, 5, and 6, we combined 0 and 1 into the category 0-1, and 5 and 6 into the category 5-6, to increase the samples size.

2.3. Medicators Ascertainment

The INFLA-score was selected as an indicator of chronic low-grade inflammation as it integrates the effect of multiple inflammatory biomarkers that reflect systemic inflammatory status[13]. The INFLA-score has also undergone validation in previous studies, where it has shown significant associations with various inflammatory conditions and chronic diseases, demonstrating its relevance and robustness as a marker for systemic inflammation[14–16]. The INFLA-score is computed based on 10-tiles of C-reactive protein (CRP), white blood cell

count (WBC), platelet count, and the neutrophil-to-lymphocyte ratio (NLR). Biomarker levels in the highest deciles (7th to 10th) are assigned values from +1 to +4, while those in the lowest deciles (1st to 4th) are assigned values from -4 to -1. The INFLA-score is the arithmetic sum of these scores, ranging from -16 to +16, where a higher score indicates a greater level of low-grade inflammation.

2.4. Outcome Ascertainment

2.4.1. Incident risk of retinal diseases

In this study, retinal diseases include AMD and RVO. Incident cases of retinal disease during follow-up were ascertained from inpatient hospital records using the International Classification of Diseases (ICD) 10 and ICD 9. Follow-up duration was calculated from the date of baseline assessment to the date of disease onset, death, or end of follow-up (30 September 2021), whichever occurred first. Baseline retinal disease was defined if participants reported that they had ever been told by a doctor that they had retinal disease using self-reported data. Individuals with such conditions at baseline were excluded. The codes for retinal diseases are shown in **sTable 1**.

2.4.2. Retinal vascular metrics from retinal photography

We measured retinal vascular morphology by using custom region-specific summarization and global physical/geometric parameters[17]. For region-specific summarization, the vascular calibers were summarized as central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE) from the 6 largest arteries and veins detected in the Standard zone, based on the revised Knudtson-Parr-Hubbard formula[18]. The artery-to-vein ratio from equivalents (AVRE) was generated by dividing CRAE by CRVE. We also used the box counting method to calculate the retinal vascular fractal dimension (FD), a measure that describes the complexity of the retinal vascular network.

2.4.3. Retinal neural metrics from optical coherence tomography

The Advanced Boundary Segmentation algorithm was utilized to segment retinal layer boundaries, identifying six layers as follows: RNFL, GCIPL, inner nuclear layer (INL) outer plexiform layer-outer nuclear layer (OPLONL), PS, and retinal pigment epithelium (RPE) [19]. We controlled the image quality by excluding images of image quality score < 40, images in the worst 10% of the internal limiting membrane[19,20]. For the analysis of each retinal layer, Individuals with retinal thickness > 2.5 standard deviations (SD) from the mean were also excluded, as previously described[19].

2.5. Covariates Assessment

The selection of covariates was based on previously published studies, as these covariates may have confounding effects on the exposure mediators, and outcomes[19]. In the AMD incidents risk analysis, covariates included age (continuous), sex (female or male), ethnicity (white, non-white), Townsend deprivation index (TDI, an area-based proxy measure for socioeconomic status), education attainment (≥college/University, <College/University). In the retinal vascular metrics analysis, we additionally included intraocular pressure (IOP) and spherical equivalent refraction (SER)[21] as covariates. In the retinal neural metrics analysis, we additionally included IOP, SER, and image quality scores as covariates.

2.6. Statistical Analysis

Descriptive statistics reported baseline characteristics of participants, where continuous variables were reported using means ± SD, and categorical variables were summarized as numbers (%). T-tests identified differences in continuous variables, while chi-squared tests compared distributions of categorical variables.

The Cox proportional hazard regression models were used to estimate the associations of healthy life scores and each healthy lifestyle behavior with retinal disease. Linear regression models were used to estimate the associations of healthy life scores and each healthy lifestyle behavior with the retinal vascular metrics and the retinal neural metrics. The linear regression models were also used to estimate the associations of healthy lifestyle score and each healthy lifestyle behavior with inflammation level among the three samples. We examined two models: (1) model 1 was adjusted for age and sex; (2) model 2 was additionally adjusted for ethnicity, TDI, and educational attainment. We additionally adjusted for SER and IOP in model 2 for the analysis of retinal vascular metrics, and adjusting for image quality score, SER, and IOP in model 2 for the analysis of retinal neural metrics. Besides, in the analysis of each healthy lifestyle behavior with retinal health indicators, we put 6 lifestyle behaviors into the models to estimate the independent associations of each healthy lifestyle behavior with retinal health.

Mediation analyses were then performed on the outcomes that were significantly associated with healthy life scores in the Cox or linear regression models. We used the following criteria to establish mediation analyses[22]: (1) healthy life score was significantly associated with the outcomes; (2) healthy life score was significantly associated with the inflammation level; (3) the inflammation level was significantly associated with the outcomes; and (4) the associations between healthy life score and the outcomes was attenuated by adjusting the inflammation level in adulthood. Furthermore, we also estimated the mediation proportion of inflammation level in the associations of each lifestyle behavior with the outcomes.

Data analyses were performed using Stata (version 17.0) and R (version 4.3.3), and all *p*-values were two-tailed, with a significance level of < 0.05.

3. Results

3.1. Population Characteristics

Of the 378,648 participants in the retinal disease samples (mean age 56.40 years, 52.23% female), the proportions of those with a score of 0-1, 2, 3, 4, and 5-6 were 8.47%, 18.98%, 28.57%, 26.09%, and 17.89%, respectively. Participants with a higher lifestyle score were younger, female, non-white, better educated, less socioeconomically deprived, and more likely to have higher proportions of healthy lifestyle behaviors and lower levels of inflammation (**Table 1**). Baseline characteristics of the populations in the retinal vascular metric samples and the retinal neural metric samples showed similar results (**sTable 2 and sTable 3**).

3.2. Associations of healthy lifestyle score and retinal neurovascular health

Figure 1 and sTable 4 showed that the overall healthy lifestyle score was associated with better retinal health in a dose-response manner. Compared with participants scored as 0-1, participants with the highest healthy lifestyle score as 5-6 showed 29% lower risk of AMD [HR (95% CI): 0.71 (0.64-0.79)], 25% lower risk of RVO [HR: 0.75 (0.57 to 0.98)], 2% increase in AVRE [β (95% CI): 0.02 (0.01 to 0.02)], 0.22 um increase in CRAE [β (95% CI): 0.22 (0.13 to 0.31)], 0.36 um decrease in CRVE [β (95% CI): -0.36 (-0.5 to -0.22)], 0.004 increase in FD [β (95% CI): 0.004 (0.002 to 0.005)], 0.38 um increase in RNFL [β (95% CI): 0.38 (0.19 to 0.56)], 0.69 um increase in GCIPL [β (95% CI): 0.69 (0.47 to 0.91)], 0.10 um increase in TNL [β (95% CI): 0.10 (0.01 to 0.19)], and 0.35 um increase in PS [β (95% CI): 0.35 (0.19 to 0.51)] (all $p_{trend} < 0.01$). For each number increment in low-risk lifestyle behavior, there was a 6% lower risk of AMD and RVO, 0.4% increase in AVRE, 0.06um increase in CRAE, 0.09 um decrease in CRVE, 0.0009 increase in FD, 0.07 um increase in RNFL thickness, 0.16 um increase in GCIPL thickness, 0.03 um increase in TNL thickness, and 0.09 um increase in PS thickness.

3.3. Associations of each lifestyle behavior with retinal neurovascular health

Table 2 shows the independent associations of each healthy lifestyle behavior with retinal indicators, adjusted for confounders and the other five lifestyle behaviors. Among the six lifestyle behaviors, maintaining a healthy body weight is an important component for retinal health, with significant associations with the maximum increase in AVRE [β (95% CI): 0.011 (0.01 to 0.01)], CRAE [β (95% CI): 0.24 (0.20 to 0.29)], FD [β (95% CI): 0.003 (0.002 to 0.003)], RNFL thickness [β (95% CI): 0.15 (0.05 to 0.24)], OPLONL thickness [β (95% CI): 0.21 (0.08 to 0.34)], and PS thickness [β (95% CI): 0.58 (0.51 to 0.66)]. Avoiding smoking showed the strongest association with the

lowest risk of AMD [HR (95% CI): 0.87 (0.83 to 0.92], as well as the maximum decrease in CRVE [β (95% CI):-0.23 (-0.29 to -0.16)]. In addition, moderate exercise is associated with the maximum increase in TNL thickness [β (95% CI): 0.08 (0.04 to 0.12)] and RPE thickness [β (95% CI): 0.12 (0.06 to 0.18)], optimal sleep duration is associated with the lowest risk for RVO [HR (95% CI): 0.79 (0.69 to 0.91)], and moderate alcohol consumption is associated with the maximum increase in GCIPL thickness [β (95% CI): 0.42 (0.31 to 0.53).

3.4. Associations of healthy lifestyle scores and each healthy lifestyle behavior with inflammation levels

Figure 2 shows that individuals with higher healthy life scores were associated with lower levels of INFLA-score, CRP, WBC, platelet count, and NLR. Great adherence to moderate physical activity, healthy diet, and optimal sleep duration significantly correlated with lower levels of all inflammation markers. Never smoking and maintaining a healthy body weight were also associated with lower levels of INFLA-score, CRP, WBC, and platelet count, but showed associations with higher levels of NLR. Conversely, moderate alcohol consumption was significantly associated with higher levels of INFLA-score, CRP, WBC, and NLR. Similar association patterns were observed when analyzing the healthy lifestyle with inflammation levels in the retinal vascular metric samples and the retinal neural metric samples (**sFigure 2 and sFigure 3**).

3.5. The mediated proportion of the INFLA-score in the associations between healthy lifestyle scores and retinal neurovascular health

Figure 3 shows that INFLA-score mediated the associations between healthy lifestyle scores and various retinal health outcomes, including and increased risk of AMD [mediated proportion (MP): 14.8%], higher AVRE (MP:12.76%), narrower CRVE (MP:24.49%), thicker GCIPL (MP:4.97%), and thicker PS (MP:26.86%). We also analyzed the mediating proportions of the INFLA-score in the associations between each healthy lifestyle behavior and retinal health indicators. For example, INFLA-score mediated the associations between moderate physical activity and low risk of AMD, higher AVRE, narrower CRVE, thicker GCIPL, and thicker RPE, with mediated proportions ranging from 9.12% to 25.19%. The detailed information is shown in **sFigure 4-sFigure 9**.

4. Discussion

This study found that participants with higher healthy life scores were associated with lower risks of AMD and RVO, and improved retinal neurovascular metrics in a dose-response manner. Specifically, maintaining a healthy body weight is a particularly important component among the six lifestyle behaviors as it was significantly associated with the maximum increase in AVRE, CRAE, FD, RNFL thickness, OPLONL thickness, and PS thickness. In addition, INFLA-score could partially explain the associations between healthy lifestyle scores and increased risk of AMD,

increased risk of RVO , decreased CRVE, increased AVRE , increased GCIPL thickness and PS thickness.

The novelty of this study is that we explored the associations between a healthy lifestyle score and retinal neurovascular health. To date, increasing evidence has emerged to investigate the connections between a combination of healthy lifestyle behaviors and beneficial health outcomes. The present study found that adopting a greater number of healthy lifestyles is significantly associated with a reduced risk of AMD and RVO. This finding aligns with a previous study using the JMDC Claims Database, which demonstrated a dose-dependent association between ideal cardiovascular health (CVH) metrics, an indicator of healthy lifestyles, and lower occurrence risk of RVO[23]. Similarly, a recent analysis from the European Eye Epidemiology Consortium reported that unfavorable lifestyle factors, primarily smoking and poor diet, increased the risk of late AMD by 2 to 2.3 times depending on genetic susceptibility[24]. Furthermore, we observed that a favorable lifestyle was associated with improved retinal vascular morphology (such as, increased AVRE, CRAE, FD, and decreased CRVE) and greater retinal thickness in the RNFL, GCIPL, TNL, and PS layers. These findings were partially supported by the Asymptomatic Poly Vascular Abnormalities Community (APAC) study, which found that a higher number of ideal CVH metrics was associated with wider arterial caliber and increased AVRE in a Chinese population[25]. Notably, the APAC study reported no significant changes in RNFL thickness or CRVE with fewer ideal CVH metrics. This discrepancy may be attributable to racial differences or variations in the definition of a healthy lifestyle. Taken together, our findings added to the growing evidence supporting the benefits of adopting multiple healthy lifestyle practices for optimal retinal health. Further studies are needed to validate these findings across diverse populations and settings to account for potential regional or demographic differences.

The mediation analyses revealed that reduced inflammation levels partly mediated the association between a healthier lifestyle and most retinal outcomes, offering deeper insights into the underlying mechanisms. Emerging evidence underscores the detrimental impact of chronic inflammation on retinal health, including its role in promoting oxidative stress, disrupting cellular homeostasis, and causing vascular and cellular damage[26]. Anti-inflammatory therapy, on the other hand, may promote retinal health by enhancing blood flow, improving the delivery of essential nutrients and oxygen to the retina, and supporting retinal function and structural integrity[27]. Healthy lifestyle factors—such as regular physical activity, healthy diet, optimal sleep duration and maintaining a healthy body weight—are known to reduce systemic inflammation[28–31]. By lowering inflammation, these lifestyle behaviors may help protect retinal cells and tissues, thus delay the onset of age-related retinal disease.

Further research is needed to confirm these pathways and clarify the specific mechanisms involved.

Our findings have significant implications for translating epidemiological evidence into actionable public health strategies. To put these findings into practice, community-based initiatives could be developed to encourage healthier lifestyle changes, such as maintaining a balanced diet, engaging in regular physical activity, quitting smoking, and managing weight-to maintain retinal neurovascular health and reduce the risk of retinal disease. Moreover, these initiatives should emphasize the importance of regular retinal health screenings, which could be integrated into broader preventive care frameworks, as the retina may serve as a non-invasive monitor of systemic disease risk. Combining information on modifiable lifestyle factors with retinal measurements may improve risk prediction for systemic disease, complementing traditional risk factor assessment and enabling more personalized prevention strategies[32].

The novelty of our study is the large-scale investigations of the different combinations of common lifestyle factors and comprehensive retinal health outcomes. However, this study has several limitations. First, we identify incident AMD cases and RVO cases using ICD codes, which potentially missed cases in which the condition was diagnosed only during outpatient visits. To mitigate this limitation, we supplemented our approach using self-reported information and record-linked data[33]. Second, the retinal neurovascular health metrics in this study primarily focused on structural indicators, such as retinal vascular caliber and thickness. Functional indicators, such as electroretinograms, were not included due to limitations in the UK Biobank data[34]. Future research is warranted to investigate the associations between healthy lifestyle factors and functional metrics of retinal health. Third, most subjects in this study were white. Therefore, the conclusions of the study need to be further verified in other races. Fourth, the INFLA-score may have some potential limitations due to its relative novelty and variability in capturing the complexity of inflammatory processes across diverse populations and chronic diseases. Additionally, the selection and weighting of biomarkers included in the INFLA-score could influence its accuracy and relevance. As a supplement, we conducted separate analyses of each inflammatory marker within the INFLA score to assess their mediating role in the association between the healthy lifestyle score and retinal health outcomes. The findings from these analyses were largely consistent with those obtained using the INFLA-score.

5. Conclusion

In conclusion, great adherence to a healthy lifestyle was associated with better retinal neurovascular health in a dose-response manner. Lower inflammation partially mediated the associations between healthy lifestyle scores and retinal

health. Our study encourages individuals to embrace healthier lifestyles, especially in terms of body weight management, to effectively maintain retinal neurovascular health and reduce the risk of retinal diseases.

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Ethics statement

The study was ethically approved by the National Information Governance Board for Health and Social Care and the NHS North West Multicenter Research Ethics Committee (reference 11/NW/0382). All participants provided informed consent during the baseline assessment. The study adhered to the principles of the Declaration of Helsinki and was conducted under UK Biobank application number 86091.

Authors' contributions

Study concept and design: Honghua Yu, Xiaomin Zeng, Danli Shi, Xianwen Shang

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Competing interests

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Availability of data and materials

Data are available in a public, open-access repository (https://www.ukbiobank.ac.uk/).

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Table 1. Baseline characteristics of the populations by Healthy lifestyle score in retinal disease samples

Baseline characteristics	Overall	0-1	2	3	4	5-6	p
Number of patients	378648 (100)	32085 (8.47)	71874 (18.98)	108162 (28.57)	98794 (26.09)	67733 (17.89)	-
Age, years, mean ± SD	56.40 ± 8.08	56.72 ± 7.76	56.60 ± 7.89	56.37 ± 8.06	56.29 ± 8.18	56.23 ± 8.29	<0.001
Sex, n (%)							<0.001
Female	197765 (52.23)	12588 (39.23)	32077 (44.63)	54296 (50.20)	56021 (56.70)	42783 (63.16)	
Male	180883 (47.77)	19497 (60.77)	39797 (55.37)	53866 (49.80)	42773 (43.30)	24950 (36.84)	
Ethnicity, n (%)							<0.001
White	359977 (95.07)	31192 (97.22)	69124 (96.17)	103000 (95.23)	93083 (94.22)	63578 (93.87)	
Non-white	18671 (4.93)	893 (2.78)	2750 (3.83)	5162 (4.77)	5711 (5.78)	4155 (6.13)	
Educational attainment, n (%)							<0.001
>=College degree	134551 (35.53)	9301 (28.99)	22276 (30.99)	36858 (34.08)	37070 (37.52)	29046 (42.88)	
<College degree	244097 (64.47)	22784 (71.01)	49598 (69.01)	71304 (65.92)	61724 (62.48)	38687 (57.12)	
TDI, mean ± SD	-1.45 ± 3.00	-1.01 ± 3.20	-1.20 ± 3.10	-1.39 ± 3.02	-1.59 ± 2.92	-1.83 ± 2.78	<0.001
Moderate physical activity, n (%)	238460 (62.98)	5751 (17.92)	30571 (42.53)	64391 (59.53)	75351 (76.27)	62396 (92.12)	<0.001
Healthy diet, n (%)	165544 (43.72)	2200 (6.86)	14652 (20.39)	39501 (36.52)	54282 (54.94)	54909 (81.07)	<0.001
Optimal sleep duration, n (%)	260165 (68.71)	8529 (26.58)	37003 (51.48)	73077 (67.56)	78877 (79.84)	62679 (92.54)	<0.001
Never smoking, n (%)	206188 (54.45)	2805 (8.74)	20073 (27.93)	53568 (49.53)	68714 (69.55)	61028 (90.10)	<0.001
Moderate alcohol consumption, n (%)	245184 (64.75)	6944 (21.64)	32213 (44.82)	67713 (62.60)	76460 (77.39)	61854 (91.32)	<0.001
Healthy bodyweight, n (%)	127827 (33.76)	1462 (4.56)	9236 (12.85)	26236 (24.26)	41492 (42.00)	49401 (72.93)	<0.001
INFLA-score	-0.42 (5.90)	1.26 (5.74)	0.59 (5.81)	-0.12 (5.84)	-0.89 (5.86)	-1.99 (5.79)	<0.001
C-reactive protein, mg/L	1.79 ± 1.69	2.33 ± 1.88	2.11 ± 1.81	1.87 ± 1.72	1.63 ± 1.58	1.31 ± 1.39	<0.001
Platelet count, 10^9/L	250.84 ± 57.24	252.00 ± 58.61	252.22 ± 58.47	251.52 ± 57.26	250.81 ± 56.75	247.79 ± 55.83	<0.001
White blood cell, 10^9/L	6.80 ± 1.70	7.26 ± 1.81	7.05 ± 1.76	6.86 ± 1.70	6.67 ± 1.64	6.43 ± 1.56	<0.001
Neutrophil-to-lymphocyte ratio	2.28 ± 0.89	2.35 ± 0.90	2.31 ± 0.89	2.29 ± 0.89	2.26 ± 0.89	2.25 ± 0.89	<0.001
Follow-up time of AMD, years, mean ± SD	12.24 (1.80)	12.06 (2.18)	12.17 (1.97)	12.23 (1.83)	12.29 (1.67)	12.33 (1.54)	<0.001
Follow-up time of RVO, years, mean ± SD	12.28 (1.73)	12.11 (2.13)	12.21 (1.90)	12.27 (1.76)	12.33 (1.58)	12.37 (1.46)	<0.001

Data are presented using means (standard deviations), or numbers (percentage). One-way ANOVA was used to test the difference of continuous variables across subgroups and $\chi 2$ for categorical variables.

Abbreviations: SD, standard deviation; TDI, Townsend Deprivation Index; AMD, age-related macular degeneration; RVO, retinal vascular occlusion.

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Table 2. Associations of each lifestyle behavior with retinal neurovascular health

Healthy lifestyle behaviors	Model 1		Model 2	
	HR or β (95% CI)	*p*	HR or β (95% CI)	*p*
Incident risk of retinal diseases[α]				
AMD incident risk				
Moderate physical activity	0.89 (0.84 to 0.94)	**<0.001**	0.89 (0.84 to 0.94)	**<0.001**
Healthy diet	0.98 (0.93 to 1.03)	0.424	0.98 (0.92 to 1.03)	0.386
Optimal sleep duration	0.97 (0.92 to 1.02)	0.268	0.99 (0.94 to 1.05)	0.722
Never smoking	0.87 (0.82 to 0.91)	**<0.001**	0.87 (0.83 to 0.92)	**<0.001**
Moderate alcohol consumption	1.02 (0.96 to 1.07)	0.601	0.99 (0.93 to 1.05)	0.684
Healthy bodyweight	0.92 (0.87 to 0.98)	**0.008**	0.94 (0.88 to 0.99)	**0.031**
RVO incident risk				
Moderate physical activity	0.86 (0.75 to 0.99)	**0.034**	0.87 (0.76 to 0.99)	**0.040**
Healthy diet	1.13 (0.99 to 1.3)	0.068	1.12 (0.98 to 1.28)	0.109
Optimal sleep duration	0.78 (0.68 to 0.89)	**<0.001**	0.79 (0.69 to 0.91)	**0.001**
Never smoking	0.92 (0.80 to 1.05)	0.227	0.91 (0.80 to 1.05)	0.193
Moderate alcohol consumption	1.18 (1.02 to 1.36)	**0.027**	1.15 (0.99 to 1.33)	0.067
Healthy bodyweight	0.82 (0.70 to 0.95)	**0.010**	0.82 (0.70 to 0.96)	**0.011**
Retinal vascular metrics[β]				
Artery-to-Vein Ratio				
Moderate physical activity	0.003 (0.001 to 0.005)	**0.001**	0.003 (0.001 to 0.005)	**0.001**
Healthy diet	0.003 (0.001 to 0.004)	**0.004**	0.002 (0.001 to 0.004)	**0.006**
Optimal sleep duration	0.001 (-0.001 to 0.003)	0.277	0.001 (-0.001 to 0.003)	0.224
Never smoking	0.001 (-0.001 to 0.003)	0.272	0.001 (-0.001 to 0.003)	0.344
Moderate alcohol consumption	0.01 (0.005 to 0.01)	**<0.001**	0.01 (0.005 to 0.01)	**<0.001**
Healthy bodyweight	0.01 (0.01 to 0.01)	**<0.001**	0.01 (0.01 to 0.01)	**<0.001**
Central Retinal Artery Equivalent, um				
Moderate physical activity	0.03 (-0.02 to 0.07)	0.243	0.01 (-0.04 to 0.05)	0.764
Healthy diet	-0.002 (-0.05 to 0.04)	0.914	-0.01 (-0.05 to 0.03)	0.711
Optimal sleep duration	0.02 (-0.03 to 0.06)	0.517	0.04 (-0.01 to 0.09)	0.084
Never smoking	-0.16 (-0.20 to -0.11)	**<0.001**	-0.12 (-0.16 to -0.08)	**<0.001**
Moderate alcohol consumption	0.25 (0.21 to 0.30)	**<0.001**	0.23 (0.19 to 0.28)	**<0.001**
Healthy bodyweight	0.21 (0.17 to 0.26)	**<0.001**	0.24 (0.20 to 0.29)	**<0.001**
Central Retinal Vein Equivalent, um				
Moderate physical activity	-0.06 (-0.13 to 0.001)	**0.055**	-0.1 (-0.17 to -0.04)	**0.002**
Healthy diet	-0.10 (-0.17 to -0.04)	**0.002**	-0.11 (-0.17 to -0.04)	**0.001**
Optimal sleep duration	-0.03 (-0.10 to 0.03)	0.322	-0.004 (-0.07 to 0.06)	0.905
Never smoking	-0.29 (-0.35 to -0.22)	**<0.001**	-0.23 (-0.29 to -0.16)	**<0.001**
Moderate alcohol consumption	0.09 (0.03 to 0.16)	**0.007**	0.07 (-0.002 to 0.13)	0.058
Healthy bodyweight	-0.15 (-0.21 to -0.08)	**<0.001**	-0.11 (-0.17 to -0.04)	**0.002**
Fractal Dimension				
Moderate physical activity	0.0004 (-0.0003 to 0.001)	0.267	0.0002 (-0.0005 to 0.001)	0.573
Healthy diet	0.001 (0.001 to 0.002)	**<0.001**	0.001 (0.0005 to 0.002)	**0.001**
Optimal sleep duration	-0.0004 (-0.001 to 0.0003)	0.306	0.0002 (-0.0005 to 0.001)	0.529
Never smoking	-0.001 (-0.002 to -0.001)	**<0.001**	-0.001 (-0.002 to -0.0004)	**0.001**
Moderate alcohol consumption	0.003 (0.002 to 0.004)	**<0.001**	0.002 (0.001 to 0.003)	**<0.001**
Healthy bodyweight	0.002 (0.002 to 0.003)	**<0.001**	0.003 (0.002 to 0.003)	**<0.001**
Retinal neural metrics[β]				
RNFL Thickness, um				

Moderate physical activity	0.04 (-0.05 to 0.13)	0.402	0.07 (-0.02 to 0.16)	0.116
Healthy diet	-0.05 (-0.14 to 0.04)	0.293	-0.04 (-0.13 to 0.05)	0.387
Optimal sleep duration	0.22 (0.13 to 0.31)	**<0.001**	0.14 (0.05 to 0.23)	**0.003**
Never smoking	0.09 (0.001 to 0.18)	**0.049**	0.01 (-0.08 to 0.09)	0.874
Moderate alcohol consumption	0.04 (-0.05 to 0.14)	0.361	0.14 (0.05 to 0.24)	**0.002**
Healthy bodyweight	0.25 (0.16 to 0.34)	**<0.001**	0.15 (0.05 to 0.24)	**0.002**
GCIPL Thickness, um				
Moderate physical activity	0.30 (0.19 to 0.41)	**<0.001**	0.18 (0.08 to 0.29)	**0.001**
Healthy diet	-0.1 (-0.21 to 0.01)	0.067	-0.06 (-0.17 to 0.04)	0.240
Optimal sleep duration	0.13 (0.02 to 0.24)	0.025	0.13 (0.02 to 0.24)	**0.023**
Never smoking	-0.10 (-0.20 to 0.01)	0.080	0.05 (-0.05 to 0.15)	0.347
Moderate alcohol consumption	0.41 (0.30 to 0.53)	**<0.001**	0.42 (0.31 to 0.53)	**<0.001**
Healthy bodyweight	0.22 (0.10 to 0.33)	**<0.001**	0.28 (0.17 to 0.39)	**<0.001**
INL Thickness, um				
Moderate physical activity	0.13 (0.09 to 0.18)	**<0.001**	0.08 (0.04 to 0.12)	**<0.001**
Healthy diet	-0.03 (-0.07 to 0.02)	0.259	0.01 (-0.03 to 0.05)	0.656
Optimal sleep duration	0.01 (-0.04 to 0.06)	0.679	0.01 (-0.03 to 0.06)	0.605
Never smoking	-0.06 (-0.1 to -0.01)	**0.016**	0.04 (-0.01 to 0.08)	0.098
Moderate alcohol consumption	0.04 (-0.01 to 0.08)	0.121	0.04 (-0.003 to 0.09)	0.068
Healthy bodyweight	-0.03 (-0.08 to 0.02)	0.216	0.02 (-0.02 to 0.07)	0.321
OPLONL Thickness, um				
Moderate physical activity	0.24 (0.11 to 0.37)	**<0.001**	0.13 (0.004 to 0.25)	**0.043**
Healthy diet	-0.14 (-0.26 to -0.01)	**0.029**	-0.04 (-0.16 to 0.08)	0.543
Optimal sleep duration	0.27 (0.14 to 0.40)	**<0.001**	0.16 (0.03 to 0.28)	**0.016**
Never smoking	-0.15 (-0.28 to -0.03)	**0.016**	0.02 (-0.10 to 0.14)	0.739
Moderate alcohol consumption	-0.39 (-0.52 to -0.26)	**<0.001**	-0.22 (-0.35 to -0.09)	**0.001**
Healthy bodyweight	0.20 (0.07 to 0.33)	**0.003**	**0.21 (0.08 to 0.34)**	**0.001**
PS Thickness, um				
Moderate physical activity	-0.11 (-0.19 to -0.02)	**0.014**	-0.03 (-0.11 to 0.05)	0.436
Healthy diet	0.10 (0.02 to 0.19)	**0.015**	0.12 (0.04 to 0.19)	**0.003**
Optimal sleep duration	0.26 (0.18 to 0.35)	**<0.001**	0.15 (0.07 to 0.23)	**<0.001**
Never smoking	0.14 (0.06 to 0.22)	**0.001**	0.11 (0.03 to 0.19)	**0.005**
Moderate alcohol consumption	-0.48 (-0.57 to -0.40)	**<0.001**	-0.38 (-0.46 to -0.30)	**<0.001**
Healthy bodyweight	0.63 (0.54 to 0.72)	**<0.001**	0.58 (0.51 to 0.66)	**<0.001**
RPE Thickness, um				
Moderate physical activity	0.15 (0.10 to 0.21)	**<0.001**	0.12 (0.06 to 0.18)	**<0.001**
Healthy diet	-0.02 (-0.08 to 0.03)	0.400	-0.04 (-0.09 to 0.02)	0.213
Optimal sleep duration	-0.13 (-0.19 to -0.07)	**<0.001**	-0.07 (-0.13 to -0.01)	**0.025**
Never smoking	-0.03 (-0.09 to 0.03)	0.315	-0.01 (-0.07 to 0.04)	0.608
Moderate alcohol consumption	-0.05 (-0.11 to 0.01)	0.133	-0.13 (-0.19 to -0.07)	**<0.001**
Healthy bodyweight	-0.06 (-0.12 to 0.004)	0.067	-0.01 (-0.07 to 0.05)	0.837

[α] The HR (95% CI) for the association of each lifestyle behaviors with retinal disease were estimated using Cox proportional hazard regression models after adjusting for age, sex, ethnicity, TDI, educational attainment and other 5 lifestyle behaviors. [β] The β (95% CI) for the association of each lifestyle behaviors with retinal vascular metrics (additionally adjusting for SER and IOP) and retinal thickness (additionally adjusting for image quality score, SER, and IOP) were estimated using linear regression models. Abbreviations: CI, confidence interval; AMD, age-related macular degeneration; RVO, retinal vascular occlusion; RNFL, retinal nerve fibre layer; GCIPL, ganglion cell-inner plexiform layer; TNL, inner nuclear layer; OPLONL, outer plexiform layer-outer nuclear layer; PS, photoreceptor segment, RPE, retinal pigment epithelium.

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