Associations of Cardiovascular Health and New-Onset Age-Related Macular Diseases From UK Biobank

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Purpose. This study aimed to investigate the correlation between cardiovascular health (CVH), evaluated through the Life's Essential 8 (LE8) score, and the risk of new-onset age-related macular degeneration (AMD).

Methods. This longitudinal analysis included 271,274 participants who were free of both cardiovascular diseases and AMD at baseline. The LE8 score was classified into three categories: low (<50 points), moderate (50 to <80 points), and high (≥80 points), with higher scores indicating better CVH. Cox proportional hazards models were used to explore the relationships between the CVH and AMD incidence. Furthermore, the population attributable risk (PAR%) was calculated for CVH and each individual metric.

Results. During an average follow-up duration of 10.9 years, a total of 7468 (2.8%) cases of AMD were documented. Individuals with moderate and high CVH levels had a 14% (hazard ratio [HR] = 0.86; 95% confidence interval [CI], 0.78–0.94) and 23% (HR = 0.77; 95% CI, 0.69-0.86) reduced risk of developing AMD, respectively. A linear dose-response relationship was identified between the cumulative LE8 score and the incidence of AMD. Attaining optimal CVH in all individuals could potentially avert 9.4% (95% CI, 3.7%–15.1%) of AMD cases. Among the CVH metrics, ideal blood glucose and blood pressure levels were related to a reduction of 3.3% and 8.7% in AMD cases, respectively.

Conclusions. Enhanced CVH is significantly associated with a reduced risk of developing AMD. Promoting CVH through the LE8 guideline might potentially contribute to the prevention of AMD.

Keywords: age-related macular diseases, cardiovascular health, Life's Essential 8

Age-related macular degeneration (AMD), the leading cause of irreversible blindness in the elderly in developed nations, is expected to affect around 288 million individuals globally by 2040.[1–3] Although genetic factors are estimated to contribute to 46% to 71% of AMD cases,[4] lifestyle factors like smoking and dietary habits have also been identified as notable risk factors for AMD development.[5–7] Exploring the modifiable factors for AMD is important because it may offer new intervention strategies to delay or prevent the onset of the disease and ultimately reduce its burden on public health.[8,9]

Although the pathogenesis of AMD is not fully understood, several studies have indicated that AMD shares a vascular disorder nature similar to atherosclerosis, which is a major cause of cardiovascular disease (CVD).[10,11] There is growing evidence indicating the associations between AMD and CVD. For instance, both conditions share common risk factors including aging, smoking, and hypertension.[12–15]

Moreover, studies have reported a higher prevalence of CVD in individuals with AMD, with patients having wet AMD showing a 26% increased risk of developing CVD compared to those without AMD.[16–18]

The Life's Essential 8 (LE8) score, introduced by the American Heart Association (AHA), is an updated algorithm for assessing cardiovascular health (CVH).[19] The LE8 score comprises four behavioral metrics (diet quality, nicotine exposure, physical activity, sleep duration) and four biological metrics (body mass index [BMI], blood pressure, lipids, and blood glucose). Given the noted co-occurrence of AMD and certain CVDs,[11,20] strategies aimed at enhancing CVH via the LE8 score could potentially contribute to AMD prevention. Nevertheless, there remains a scarcity of research exploring the correlation between adherence to CVH as assessed by the LE8 score and the occurrence of AMD.

Therefore the objective of this study is to investigate the association between CVH, as estimated by the LE8 score, and the occurrence of AMD. Furthermore, we intend to evaluate the potential effects of a hypothetical decrease in adherence to CVH on AMD incidence.

Methods

Study Population

The data for this study was derived from the UK Biobank, a large, ongoing prospective study. The UK Biobank enrolled more than 500,000 participants aged 37 to 73 years from various regions of the United Kingdom between 2006 and 2010. Participants provided detailed information regarding their sociodemographic factors, lifestyle habits, and health-related details through touchscreen questionnaires, physical examinations, and the collection of biological samples. All ocular examinations were conducted by trained personnel to ensure that the measurements were taken systematically according to standard operating procedures or instructions.[21] The study design and methodology have been previously documented.[22–24]

For this study, participants with missing data on LE8 components (N = 214,473) were initially excluded. Subsequently, individuals with prevalent CVD (N = 13,777) or AMD (N = 2724) at baseline were further excluded. Finally, a total of 271,274 participants were included in the longitudinal analyses (Supplementary Fig. S1). This study has been conducted using the UK Biobank Resource under Application Number 91320.

Follow-Up and AMD Incident Cases

Participants without a history of AMD and CVD at baseline were followed up from the time of recruitment until the occurrence of incident AMD, death, loss to follow-up, or the end of follow-up (December 31, 2020, for England and Wales and January 18, 2021, for Scotland), whichever came earlier. Participants were followed up through two main methods: periodical online questionnaire assessments and access to electronic health records including primary care, hospital inpatient records, and national cancer and death registries. AMD cases were identified via health records using the ICD10 code H353, ICD9 code 3625, verbal interviews conducted by trained staff (field code 20002 [1528]), and touchscreen questionnaires (field codes 6148 and 5923). Details about self-reported data were listed in Supplementary Table S1.

LE8 Score

According to the definition of the AHA, the LE8 score comprises four behavior metrics (diet, physical activity, nicotine exposure, sleep health) and four biological metrics (BMI, blood lipids, blood glucose, and blood pressure).[19] Details about the scoring methods used for each cardiovascular metric was shown in Supplementary Table S2. In this study, the healthy diet score was evaluated through the administration of the baseline touchscreen questionnaire. The criteria for assessing the healthy diet score were modified from the AHA recommendations to ensure compatibility with the available data in the UK Biobank.[25,26] The detailed scoring process for the healthy diet score is present in Supplementary Table S3.

Each metric is scored on a scale from 0 to 100 points, and the average score is calculated by summing the scores for all metrics and dividing by eight. The LE8 score was classified into three groups: low (<50 points), moderate (50 to <80 points), and high (≥80 points), with a higher score indicating better CVH.[19]

Covariates

Study covariates were measured during the initial assessment, including age, sex, ethnicity, Townsend Deprivation Index (TDI), educational level, household income, and drinking status. The diagnosis of CVD was obtained using linked hospital admission data in the UK Biobank. The resource and definition of the covariates are listed in Supplementary Table S4.

Statistical Analyses

The baseline characteristics of the study participants were reported as means (standard deviation [SD]) for continuous variables and as percentages for categorical variables across strata of LE8 (low, moderate, and high CVH). Differences between groups were assessed using either ANOVA test or χ^2 test.

The cumulative incidence of AMD was calculated using the Kaplan-Meier method with the log-rank test, stratified by three levels of LE8 score. Cox proportional hazards regression models were used to evaluate the association between CVH and AMD. Hazard ratios (HR) and their corresponding 95% confidence intervals (CI) were calculated for the three categories of LE8. Model 1 included covariates of age, sex, and ethnicity. Model 2 further adjusted for educational level, TDI, household income and drinking status based on Model 1. Additionally, we performed restricted cubic spline (RCS) analyses with four knots to assess the dose-response relationship between LE8 score and risk of AMD. Moreover, to estimate the potential reduction in AMD cases if all individuals were in the high CVH category, we calculated the population attributable risk percent (PAR%).[27]

Furthermore, we investigated the correlation between each individual LE8 component and the risk of AMD. Each LE8 components were categorized into binary groups: non-ideal and ideal. Optimal condition was defined as achieving a diet score in the 95th percentile, engaging in physical activity of ≥600 metabolic equivalent-min/week, being a non-smoker, maintaining a sleep duration of seven to less than nine hours per day, having a BMI below 25, keeping non-high-density lipoprotein (HDL) cholesterol levels under 130 mg/dL, sustaining HbA1c levels below 7.0%, and having

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blood pressure below 120/80 mm Hg.[28] Moreover, all eight variables were mutually adjusted when considering covariates in the multivariate model. PAR for each metric was also calculated.

Subgroup analyses were performed to investigate the association stratified by age (<60 and ≥ 60 years), sex (female and male), ethnicity (white and others), TDI (quintiles 1, quintiles 2–4, quintile 5), education level (college/university degree and others), household income (<£18,000, £18,000–£51,999, and ≥£52,000) and drinking status (current and previous/never). Several sensitivity analyses were conducted. First, we conducted additional adjustments for the polygenic risk score for AMD obtained from the UK Biobank. Second, because aging is the most significant risk factor associated with AMD, we repeated the primary analysis by restricting participation to individuals over 50 years old. Third, multiple imputations were used to handle missing values on covariates. Fourth, individuals with follow-up time less than two years were excluded. Last, to assess the contribution of blood lipid metrics to AMD in the LE8 score, new LE8 scores were reconstructed by omitting blood lipid. All statistical analyses were conducted using R software version 4.3.1. Statistical significance was defined as a two-tailed P value < 0.05.

Results

Baseline Characteristics of the Participants

This study included a total of 271,274 participants. The mean (SD) age of the study population was 55.9 (8.1) years. In total, 143,718 (53%) of the participants were female. The average LE8 score among participants was 68.1. Specifically, 18,981 (7.0%), 206,500 (76.1%), and 45,793 (16.9%) participants were classified into the low, moderate, and high CVH categories, respectively.

The baseline characteristics of study participants categorized by CVH groups are presented in Table 1. Participants with high CVH, in contrast to those with lower CVH, were more likely to be younger, female, non-smoking status, had higher educational levels, higher household income, better diet score, longer sleep duration, higher levels of moderate and vigorous physical activity, lower BMI, HbA1c, systolic and diastolic blood pressure, non-HDL cholesterol, and TDI.

Cardiovascular Health and Age-Related Macular Diseases

After a mean follow-up period of 10.9 years, 7468 (2.8%) of participants developed AMD. Of the cases identified, 1178 (15.8%) were through self-reported data, whereas 6290 (84.2%) were identified through medical records. The Kaplan-Meier curves revealed a significant association between lower LE8 score and an increased incidence of AMD (P for log rank test < 0.0001; Fig. A). Additionally, the RCS analysis revealed a significant linear trend (P < 0.001) indicating that higher LE8 score were associated with a lower risk of incident AMD (Fig. B). As shown in Table 2, after adjusting for all covariates, the HRs (95% CIs) for AMD were as follows: 1.00 (reference) for the low-CVH category, 0.86 (0.78, 0.94) for the moderate-CVH category, and 0.77 (0.69, 0.86) for the high-CVH category. An SD increase in LE8 score was associated with a 5% decreased risk of AMD (95% CI, 0.92-0.97). Furthermore, in the present population,

Table 1. Baseline Characteristics According to the Categories of Cardiovascular Health

Characteristics	Low CVH	Moderate CVH	High CVH	*P* Value
Number of participants	18,981	206,500	45,793	
Age, y	56.4 (7.7)	56.5 (8.0)	53.1 (8.2)	<0.001
Female	8030 (42.3%)	104,451 (50.6%)	31,237 (68.2%)	<0.001
White	17,906 (94.3%)	196,578 (95.2%)	43,716 (95.5%)	<0.001
Townsend deprivation index	−0.6 (3.3)	−1.5 (3.0)	−1.7 (2.8)	<0.001
College/university degree	4495 (23.7%)	72,456 (35.1%)	21,516 (47.0%)	<0.001
Income				<0.001
<£18,000	4944 (26.0%)	36,317 (17.6%)	5651 (12.3%)	
£18,000–£51,999	8246 (43.4%)	96,328 (46.6%)	20,680 (45.2%)	
≥£52,000	3641 (19.2%)	51722 (25.0%)	14,923 (32.6%)	
Drinking status				<0.001
Current	17,300 (91.1%)	192,700 (93.3%)	42,495 (92.8%)	
Former	960 (5.1%)	6357 (3.1%)	1359 (3.0%)	
Never	707 (3.7%)	7344 (3.6%)	1925 (4.2%)	
Smoking status				
Never	5179 (27.3%)	111,066 (53.8%)	35,011 (76.5%)	
Previous	7370 (38.8%)	75,985 (36.8%)	10,037 (21.9%)	
Current	6432 (33.9%)	19,449 (9.4%)	745 (1.6%)	
Moderate activity, MET-min/week	402.9 (954.0)	959.3 (1227.5)	1046.5 (1180.8)	
Vigorous activity, MET-min/week	248.7 (893.9)	680.1 (1168.6)	896.8 (1204.6)	
Healthy diet score	2.8 (1.2)	3.7 (1.5)	4.8 (1.3)	
Sleep duration (h/d)	6.9 (1.6)	7.2 (1.0)	7.3 (0.8)	
BMI	32.1 (5.6)	27.4 (4.3)	23.8 (2.8)	
SBP (mm Hg)	149.3 (18.2)	141.6 (18.9)	124.5 (15.3)	
DBP (mm Hg)	88.8 (10.3)	83.4 (10.2)	74.6 (8.7)	
Non-HDL cholesterol (mg/dL)	188.9 (43.5)	169.4 (39.6)	138.4 (30.9)	
HbA1c	5.8% (0.9)	5.4% (0.5)	5.2% (0.3)	
LE8 score	43.5 (5.5)	66.6 (7.7)	85.2 (4.3)	

DBP, diastolic blood pressure; HbA1c: glycated hemoglobin A1c; MET, metabolic equivalent of task; SBP, systolic blood pressure.

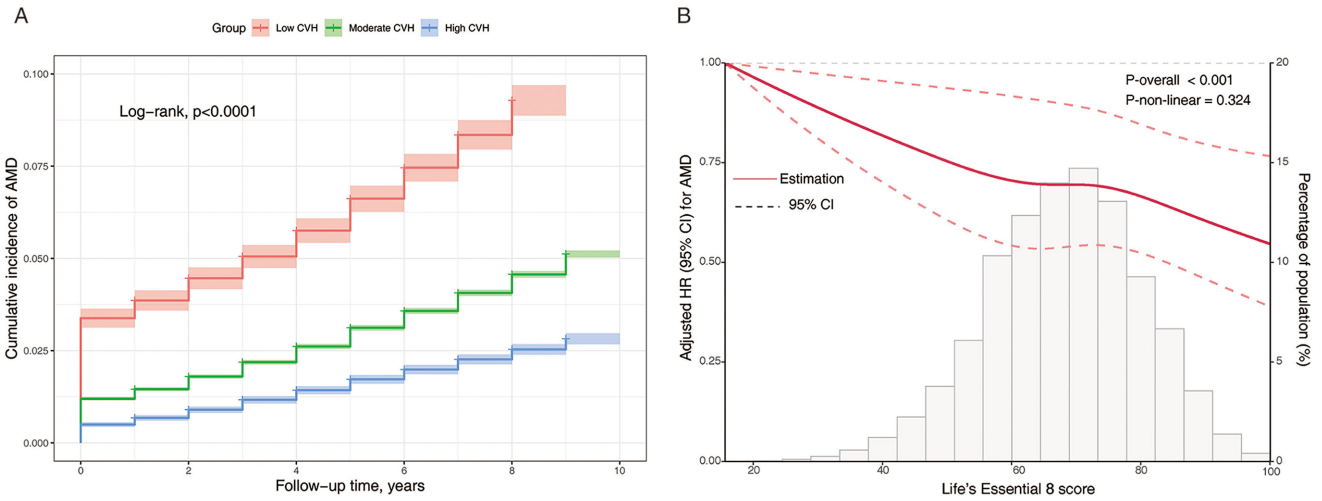

Figure. Cumulative incidence of AMD by cardiovascular health categories **(A)**. Dose-response relationship of LE8 and risk of incident AMD by RCS analysis **(B)**. RCS analysis was derived from Cox proportional-hazards models adjusted for age, sex, ethnicity, educational level, household income, Townsend index, drinking status.

Table 2. Associations Between Cardiovascular Health* and Risk of Incident Age-Related Macular Diseases

			Model 1†		Model 2‡	
CVH	**N**	**Events (%)**	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Low	18,981	598 (3.2)	Reference		Reference	
Moderate	206,500	5918 (2.9)	0.83 (0.77–0.91)	<0.001	0.86 (0.78–0.94)	0.001
High	45,793	952 (2.1)	0.76 (0.69–0.84)	<0.001	0.77 (0.69–0.86)	<0.001
Per SD increment in LE8			0.95 (0.92–0.97)	<0.001	0.95 (0.92–0.97)	<0.001
PAR, 95% CI			8.5% (3.2–13.9)		9.4% (3.7–15.1)	

* Cardiovascular health was assessed by Life's Essential 8 which includes four health behaviors: diet, physical activity, nicotine exposure, sleep health; and four health factors: BMI, blood lipids, blood glucose, and blood pressure.
† Adjusted for age, sex, and ethnicity.
‡ Additionally adjusted for Townsend deprivation index, education levels, household income and drinking status based on Model 1.

9.4% (95% CI, 3.7–15.1) of new-onset AMD might have been prevented if all individuals have a high CVH.

LE8 Metrics and AMD

Table 3 presents the association between each LE8 metric and incident AMD. In the behavior subscale, maintaining an ideal level of physical activity was associated with a 7% reduction in the risk of AMD development (HR = 0.93; 95% CI, 0.88–0.98; PAR = 2.7%). The biological subscale revealed significant associations between AMD development and blood lipids, blood glucose, and blood pressure. Optimal levels of blood glucose (HR = 0.41; 95% CI, 0.37–0.45; PAR = 3.3%) and blood pressure (HR = 0.89; 95% CI, 0.82–0.97; PAR = 8.7%) were correlated to a decreased risk of AMD development. Conversely, maintaining ideal blood lipid levels was associated with an 18% increased risk of AMD (HR = 1.18; 95% CI, 1.12–1.26; PAR = −13.7%).

Subgroup and Sensitivity Analyses

Several subgroup analyses were conducted. The associations between LE8 and the incidence of AMD were found to be more pronounced in areas with higher levels of deprivation (*P* for interaction <0.05, Supplementary Table S5). There were no significant modifying effects of sex, age, ethnicity, education levels, household income, or drinking status on the relationship between LE8 scores and AMD (Supplementary Table S5). Additionally, after additional adjustment for polygenic risk score for AMD (Supplementary Table S6) and limiting the analysis to participants over 50 years old (Supplementary Table S7), the findings are still consistent. The results showed consistency even after conducting multiple imputation analyses for covariates with missing data (Supplementary Table S8), excluding participants with less than a two-year follow-up period (Supplementary Table S9), replicating the analysis solely for AMD cases defined by ICD-10 code (Supplementary Table S10), or excluding blood lipids (Supplementary Table S11).

Discussion

In this study, we identified a significant association between CVH, as assessed by the LE8 score, and the occurrence of AMD among the 271,274 participants. Individuals with moderate and high CVH had a 14% and 23% lower risk, respectively, of developing incident AMD compared to those with low CVH. We observed a linear dose-response associa-

Table 3. The Association of Cardiovascular Health Metrics and the Incidence of Age-Related Macular Diseases

	Model 1*		Model 2†		
Component of LE8	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**	**PAR (%, 95% CI)‡**
Diet					0.7 (−5.0 to 6.5)
Non-ideal	Reference		Reference		
Ideal	0.99 (0.93, 1.05)	0.670	0.99 (0.92, 1.06)	0.777	
Physical activity					2.7 (0.8 to 4.6)
Non-ideal	Reference		Reference		
Ideal	0.93 (0.89, 0.98)	0.004	0.93 (0.88, 0.98)	0.005	
Tobacco exposure					1.2 (−1.1 to 3.5)
Non-ideal	Reference		Reference		
Ideal	0.96 (0.92, 1.01)	0.109	0.97 (0.93, 1.02)	0.312	
Sleep health					0.2 (−1.4 to 1.8)
Non-ideal	Reference		Reference		
Ideal	1.00 (0.95, 1.05)	0.848	0.99 (0.94, 1.05)	0.799	
BMI					1.1 (−2.4 to 4.6)
Non-ideal	Reference		Reference		
Ideal	0.98 (0.93, 1.03)	0.330	0.99 (0.93, 1.04)	0.590	
Blood lipids					−13.7 (−18.9 to −8.5)
Non-ideal	Reference		Reference		
Ideal	1.18 (1.12, 1.25)	<0.001	1.18 (1.12, 1.26)	<0.001	
Blood glucose					3.3 (2.7 to 3.9)
Non-ideal	Reference		Reference		
Ideal	0.41 (0.37, 0.45)	<0.001	0.41 (0.36, 0.46)	<0.001	
Blood pressure					8.7 (1.8 to 15.7)
Non-ideal	Reference		Reference		
Ideal	0.92 (0.85, 0.99)	0.033	0.89 (0.82, 0.97)	0.011	

* Adjusted for age, sex, and ethnicity.
† Additionally adjusted for Townsend deprivation index, education levels, household income and drinking status based on Model 1. For analyses on individual LE8 components, other components were further adjusted.
‡ Adjusted for covariates based on Model 2.

tion between the LE8 score and the incidence of AMD. Moreover, the adjusted PAR% indicated that 9.4% of AMD cases could potentially be prevented if all participants were able to attain a high CVH level.

In our study, 2.8% of the 7468 participants developed AMD over an average follow-up period of 10.9 years, a notably lower rate compared to findings in other studies.[29,30] This disparity could be attributed to the "healthy volunteer" bias and the younger age of participants in the UK Biobank. Meanwhile, the low response rate of 5.5% in the UK Biobank may result in the underdiagnosis of AMD, contributing to the low incidence rates observed in this study. However, it is unlikely that the direction of the association differs between respondents and non-respondents, so representativeness is not a major concern.[21] Furthermore, there was no significant difference in AMD incidence between White and non-White populations (2.76% and 2.65%, respectively). Previous research indicated that AMD incidence was highest among Whites, ranging from 2.73% to 5.3%, considerably surpassing other ethnic groups.[31,32] These discrepancies may stem from the fact that only 5% of our study participants were non-White, and they shared similar environmental factors because of their common UK origin.

Studies have demonstrated a significant correlation between elevated LE8 scores and a decreased risk of cardiovascular events, including myocardial infarction, heart failure, and stroke.[33–35] These results underscore the importance of the LE8 score in enhancing CVH and its efficacy in identifying individuals at high risk of CVD. Previous research has documented the established association and shared risk factors between AMD and CVD.[36–39] The LE8 score provides a comprehensive assessment of CVH and was first utilized to offer novel perspectives for AMD prevention. Our study has revealed a significant correlation between LE8 score and the risk of AMD, indicating that the LE8 score is valuable not only for CVH assessment but also holds promise in preventing AMD by enhancing overall health. Moreover, the LE8 score offers a user-friendly method to monitor and enhance health-related risk factors, potentially resulting in improved health outcomes and decreased risks of both CVD and AMD. Furthermore, our results demonstrate that with each SD increase in LE8, there is a substantial 5% decrease in the risk of developing AMD. In alignment with the recommendations of the AHA, our findings advocate for a gradual adjustment of health-related risk factors to enhance health outcomes.[19]

Although the certainty of the association between all components of LE8 and AMD remains uncertain, previous research has investigated each individual element. Studies have identified associations between AMD and lifestyle factors, including behavioral metrics within the LE8 framework such as diet, physical activity, sleep, and smoking.[40–45] Consistent with existing literature,[46–49] our findings suggest that maintaining an optimal level of physical activity may reduce the risk of AMD development. However, our study did not find significant correlations between the other behavioral components of the LE8 score and AMD. Regarding biological indicators, in line with previous studies,[50,51] our results suggested a positive association between blood glucose levels and AMD. Individuals with diabetes mellitus demonstrated a higher susceptibility to developing AMD,[52,53] underscoring the importance of effectively

managing blood glucose for AMD prevention. Additionally, our research uncovered a notable correlation between blood pressure levels and AMD incidence. Maintaining an ideal blood pressure level was related to an 11% decrease in AMD risk, aligning with the findings of Hyman et al.[54] Systemic hypertension could impact choroidal blood flow, potentially contributing to AMD progression and choroidal neovascularization.[55] Furthermore, our results are consistent with previous evidence, suggesting that HDL cholesterol may elevate the likelihood of AMD development.[56,57] Collectively, these findings reinforce the identified correlations between the composite LE8 score and incident AMD, suggesting that maintaining optimal CVH could help mitigate the impact of AMD.

The current study had several limitations. First, the diagnosis of AMD relied on self-reported data and hospital records obtained from the UK Biobank, and information regarding specific subtypes of AMD, such as dry and wet AMD, was not available. Previous research has indicated that different subtypes of AMD may demonstrate varying associations with CVD.[58,59] However, it remains unclear whether cardiovascular risk factors exert differential effects on distinct subtypes of AMD. Second, the lack of a specific definition for age-related maculopathy means that early or less-severe cases of macular degeneration might not be captured, potentially resulting in the omission of diagnosed AMD cases. Additionally, it would have been valuable to determine whether any of the participants had a family history of AMD; however, this information was not available in the UK Biobank. Third, individuals with low CVH may have more frequent interactions with healthcare providers, which could lead to higher detection rates of other conditions, such as AMD, thereby potentially exaggerate the incidence of AMD within the low CVH population. Nonetheless, questionnaires and ocular measurements were repeated every two to three years in subsets of participants, with follow-up intervals being the same for all participants in the cohort, regardless of their CVH status.[60] Fourth, the evaluation of the behavioral components in the LE8 score relied on self-reported data, which introduces the possibility of recall bias. Fifth, we did not examine the relationship between changes in CVH over time and the incidence of AMD, because the majority of CVH information was only collected at the baseline. Nevertheless, previous studies have indicated that CVH levels exhibit stability or decline over time.[61] Sixth, despite comprehensive adjustments for potential confounding factors, it is not feasible to entirely eliminate the potential for residual confounding. Seventh, as an observational study, our findings do not establish sufficient evidence to establish a causal relationship. Therefore the PARs should be interpreted with caution. Last, although the UK Biobank is subject to a "healthy volunteer" selection bias and the majority of participants in our study were of White ethnicity, caution is warranted when generalizing these findings to other demographic groups. However, research has shown that exposure-disease relationships in UK Biobank can still be widely generalizable, even if the study population is not perfectly representative.[62]

In conclusion, our results demonstrate a significant association between elevated CVH, as evaluated by the LE8 score, and a decreased risk of developing AMD. Promoting CVH through adhering to the LE8 guidelines may offer a potential strategy for preventing the onset of AMD.

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