Association of Retinal Age Gap With Arterial Stiffness and Incident Cardiovascular Disease

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BACKGROUND: Retinal parameters could reflect systemic vascular changes. With the advances of deep learning technology, we have recently developed an algorithm to predict retinal age based on fundus images, which could be a novel biomarker for aging and mortality. Therefore, we aim to investigate associations of retinal age gap with arterial stiffness index and incident cardiovascular disease (CVD).

METHODS: A deep learning model was trained based on 19,200 fundus images of 11,052 participants without any medical history at baseline to predict the retinal age. Retinal age gap (retinal age predicted minus chronological age) was generated for the remaining 35,917 participants. Regression models were used to assess the association between retinal age gap and arterial stiffness index. Cox proportional hazards regression models and restricted cubic splines were used to explore the association between retinal age gap and incident CVD.

RESULTS: We found each 1-year increase in retinal age gap was associated with increased arterial stiffness index (β=0.002 [95% CI, 0.001–0.003]; P<0.001). After a median follow-up of 5.83 years (interquartile range: 5.73–5.97), 675 (2.00%) developed CVD. In the fully adjusted model, each 1-year increase in retinal age gap was associated with a 3% increase in the risk of incident CVD (hazard ratio=1.03 [95% CI, 1.01–1.06]; P=0.014). In the restricted cubic splines analysis, the risk of incident CVD increased significantly when retinal age gap reached 1.21 (hazard ratio=1.05 [95% CI, 1.00–1.10]; P-overall<0.0001; P-nonlinear=0.0681).

CONCLUSIONS: We found that retinal age gap was significantly associated with arterial stiffness index and incident CVD events, supporting the potential of this novel biomarker in identifying individuals at high risk of future CVD events.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: aging ■ cardiovascular disease ■ retina ■ vascular stiffness

Among noncommunicable diseases, cardiovascular disease (CVD) is the leading cause of morbidity and mortality globally. From 2005 to 2015, global CVD deaths increased by 12.5% to 179 million per year.1 Approximately 1 in 3 deaths worldwide can be attributed to CVD.2 Driven by an aging and growing population, the burden of CVD is projected to increase further.

Prevention and early detection of CVD are crucial in reducing CVD morbidity and mortality.3 Many CVD risk calculators have thus been developed, including the Cardiovascular Risk Score, Systemic Coronary Risk Evaluation, and Framingham risk score.4–7 Nevertheless, these risk prediction models are limited by lack of precision, information bias for...
questionnaire-based models, and the involvement of invasive procedures.8-10

The retina is highly vascular and easily accessible by noninvasive imaging and assessments and can serve as a surrogate measure of the health of the systemic vasculature. Collective evidence has demonstrated that fundus images contain valuable information on cardiovascular health. Changes in retinal vascular parameters derived from fundus images, such as wider retinal venules and narrower retinal arterioles, have been found to be independent predictors of future CVD risk.11-18 The advent of deep learning (DL) has greatly improved the efficacy and accuracy of extracting salient features from images. Recent studies have demonstrated the predictive value of retinal fundus images on CVD risk profiles and atherosclerosis via DL algorithms (DLA).19-21

To maximally utilize available information from the retina, we have developed a DLA that can accurately predict an individual’s chronological age from fundus images. The retinal age gap (defined as fundus image predicted age minus chronological age) was found in our previous study to be associated with an increased risk of mortality, further lending credence to its potential as a robust biomarker of aging.22 Age is one of the most important risk factors for atherosclerosis and CVD, with CVD risk increasing exponentially with age.23,24 Therefore, we hypothesized that retinal age gap may have the potential to be a novel biomarker for future CVD risk.

Herein, we aimed to investigate the association of the retinal age gap with the arterial stiffness index (ASI). As the arterial system ages, large arteries undergo progressive elastic and collagenous remodeling that result in increased stiffness. ASI is an accepted, noninvasive measure of cardiovascular health, and an indicator of subclinical CVD.25 Further, we also investigated the relationship of the retinal age gap with the future risk of incident CVD based on the UK Biobank study.

METHODS

The UK Biobank data are available on application to access (http://www.ukbiobank.ac.uk/).

Study Population

The UK Biobank is a large-scale prospective study with over 500 000 participants aged 40 to 69 years recruited between 2006 and 2010. This study has collected extensive phenotypic and genotypic data of each participant with their informed consent. All participants completed questionnaires on their lifestyle, environment and medical history, underwent physical and functional measurements, and provided blood, urine and saliva samples. Ophthalmic examinations including retinal photographs were introduced in 2010. Health-related events were recorded via linkage with Hospital Episode Statistics (HES) and death registers. A detailed description of the UK Biobank data and protocols can be found elsewhere.26

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.27 The North West Multi-centre Ethics Committee granted ethical approval to the UK Biobank (11/NW/0382). The current study operates in accordance with the principles of the Declaration of Helsinki, with written informed consent from all participants, under the UK Biobank application number 62489.

Fundus Photography

The physical measures of ophthalmic examination included LogMAR visual acuity, autorefraction and keratometry (Tomey RC5000, Tomey GmbH, Nuremberg, Germany), intraocular pressure (IOP, Ocular Response Analyzer, Reichert, New York), and paired retinal fundus and optical coherence tomography imaging (OCT, Topcon 3D OCT 1000 Mk2, Topcon Corp, Tokyo, Japan). A 45-degree nonmydriatic and nonstereoscopic fundus image centered to include both the optic disc and the macula was taken for each eye. In total, 131 238 images from 66 500 participants collected at the baseline were obtained from the UK Biobank study.

Arterial Stiffness

The ASI was derived from the analysis of the digital volume pulse, an indirect method to assess AS peripherally. ASI data were collected at baseline via the PulseTrace PCA 2 (CareFusion), which uses finger photoplethysmography to assess the pulse waveform using an infrared sensor placed on the index finger of the participant’s dominant hand. The pulse waveform comprises a systolic peak and a second diastolic peak, and the transit time (peak-to-peak time [PPT]) between the 2 peaks is related to the time it takes for the pulse wave to travel through the peripheral arterial tree. The length of this arterial tree path is proportional to a person’s height (h), enabling the calculation of an index of large artery stiffness using the formula ASI=h/PPT. The ASI was natural log transformed.

CVDAscertainment

To ascertain CVD events, the date of the first known myocardial infarction or stroke was identified via linkage with hospital admission data in England, Scotland, and Wales, the national death register data and self-reporting. Myocardial infarction was defined by codes 410, 411, 412.X, 429.79 in the 10th edition of International Classification of Diseases (ICD-9), and codes I21, I22, I23, I24.1 or I25.2 in the 10th edition of ICD-10. Stroke was defined by ICD-9 codes 430.X, 431.X, 434.X, 434.0, 434.1, 434.9, 436.X, and ICD-10 codes I60, I61, I63, or I64.X. History of CVD events was defined as the occurrence of CVD events before the baseline examination. Incident CVD events were defined as the first occurrence of CVD events during the follow-up period, from the baseline examination to...
February 29, 2016, or the first occurrence of either myocardial infarction or stroke. Participants who are lost to follow-up were censored. Participants with a history of CVD events were excluded from the analysis of the association between retinal age gap and incident CVD.

Deep Learning Model for Age Prediction
A total of 80,169 images from 46,969 participants passed the image quality check. The details of quality check have been documented elsewhere. Briefly, the fundus images were rated by 2 ophthalmologists as good, usable, or rejected based on a 3-level quality rating system, which took into account 4 quality indicators including blurring, uneven illumination, low-contrast, and artifacts. Among 46,969 participants, 11,052 participants did not report any previous disease. A total of 19,200 fundus images from 11,052 participants without any medical histories at baseline were used to train the DL model for age prediction. Images from both eyes if available were used to maximize the volume of data available. Among the remaining 35,917 participants, 35,541 with available ASI data and its value within 4 standard deviations (SDs) of the mean (N=376) were included to investigate the association between retinal age gap and ASI. A total of 33,817 participants who had no history of CVD events at baseline were included to investigate the association between retinal age gap and incident CVD. Five knots were placed at different quintiles and ASI. For the logistic regression models, we dichotomized the outcomes into ASI equal to/above or below the median ASI. An ASI equal to or above the median ASI was defined as a severe ASI. We investigated the effect of a 1-year increase in retinal age gap on the odds ratio of having a severe ASI. The following covariates—baseline age, sex, and ethnicity (model I); additional Townsend deprivation indices, educational level, smoking status, drinking status, physical activity level, history of CVD events, metabolic syndrome, and general health status (model II) were adjusted for in the regression models.

Covariates
Confounding factors included baseline age, sex, ethnicity (recorded as white or nonwhite), Townsend deprivation indices (an area-based proxy measure for socioeconomic status), education attainment (recorded as college/university degree and above, or others), smoking status (recorded as current/previous or never), drinking status (recorded as current/previous or never), physical activity level (recorded as above physical education recommendation or not), history of CVD events (for the association between ASI and the retinal age gap), metabolic syndrome, and general health status (recorded as excellent/good and fair/poor). We further adjusted for ASI in the analysis of the association between retinal age gap and incident CVD. According to the National Cholesterol Education Program adult treatment panel III guidelines (NCEP ATP III), metabolic syndrome was defined as the presence of 3 or more of the following factors: unhealthy waist circumference, hypertension, dyslipidemia, hypertriglyceridemia, and hyperglycemia. We used established reference values for women (≥88 cm) and men (≥102 cm) as cutoff values to define unhealthy waist circumference. Hypertension was defined as a systolic blood pressure of 130 mm Hg or above, a diastolic blood pressure of 85 mm Hg or above or the use of antihypertensive drugs. Dyslipidemia was defined as a high-density lipoprotein cholesterol level of <40 mg/dL among men and <50 mg/dL among women. Hypertriglyceridemia was defined as triglyceride levels of 150 mg/dL or greater. Hyperglycemia was defined as fasting blood glucose levels >110 mg/dL or taking medications/insulin for diabetes.

Statistical Analyses
Descriptive statistics, including means and SDs, numbers and percentages, were used to report baseline characteristics of study participants. Participants without available ASI data or with an ASI value beyond mean±4SD were excluded (Figure S1). Linear regression models considering retinal age gap as a continuous linear term were fitted to investigate the association between a 1-year increase in retinal age gap and ASI. We then investigated the associations between retinal age gaps of different quintiles and ASI. For the logistic regression models, we dichotomized the outcomes into ASI equal to/above or below the median ASI. An ASI equal to or above the median ASI was defined as a severe ASI. We investigated the effect of a 1-year increase in retinal age gap on the odds ratio of having a severe ASI. The following covariates—baseline age, sex, and ethnicity (model I); additional Townsend deprivation indices, educational level, smoking status, drinking status, physical activity level, history of CVD events, metabolic syndrome, and general health status (model II) were adjusted for in the regression models.

Cox proportional hazards regression models were used to explore the relationship between retinal age gap (continuous or quintiles) and incident CVD. We adjusted Cox proportional hazards regression models for the following covariates—baseline age, sex, and ethnicity (model I); additional Townsend deprivation indices, educational level, smoking status, drinking status, physical activity level, history of CVD events, metabolic syndrome, and general health status (model II); additional ASI (III).

The proportional hazards assumption for each variable included in the Cox proportional hazards regression models were assessed graphically. Restricted cubic spline analyses were performed to further assess the association between retinal age gap and incident CVD. Five knots were placed at equal intervals across the distribution of the retinal age gap. Retinal age gap of zero years was used as the reference. All variables were found to meet the assumption. Variance inflation factors (VIF) procedure was used to test collinearity for all variables and all covariates’ variance inflation factor were <2 (mean: 1.16). A 2-sided P < 0.05 indicated statistical significance. Analyses were performed using Stata (version 13, StataCorp, TX).
RESULTS

Study Sample
The baseline characteristics of 35,541 included participants were shown in Table 1. The mean age was 56.8±8.04 years, and 55.6% were females.

Retinal Age Gap and Arterial Stiffness Index
Linear regression models were implemented for the investigation of the retinal age gap and continuous ASI. We found that a 1-year increase in the retinal age gap was associated with a significant increase in ASI with a β coefficient of 0.002 ([95% CI, 0.001–0.003]; \(P=0.001\)) after adjusting for all included confounders. When the participants were divided into quartiles by their retinal age gaps, those in the second (\(β=0.013\) [95% CI, 0.002–0.023]; \(P=0.018\)), third (\(β=0.018\) [95% CI, 0.007–0.029]; \(P=0.002\), and fourth (\(β=0.017\) [95% CI, 0.004–0.030]; \(P=0.009\)) quartiles had significantly higher ASI values compared with those in the first quartile (Table 2).

Considering ASI as a categorical variable, logistic regression models indicated higher odds of having severe ASI with a larger retinal age gap. The odds ratio of having severe ASI was 1.01 ([95% CI, 1.01–1.02]; \(P<0.001\)) with each 1-year increase in the retinal age gap when adjusting for all included confounders. It was shown that participants in the third (odds ratio=1.16 [95% CI, 1.07–1.25]; \(P<0.001\)) and fourth (odds ratio=1.16 [95% CI, 1.07–1.26]; \(P=0.001\)) quartiles had significantly higher odds of having severe ASI compared with those in the first quartile.

Table 1. Baseline Characteristics of Study Participants Stratified by Quartiles of Retinal Age Gap

| Baseline characteristics | Missing (N) | Total | Q1 | Q2 | Q3 | Q4 | P value |
|-------------------------|-------------|-------|-----|-----|-----|-----|---------|
| N                       | 35 541      |       |     |     |     |     |         |
| Age, mean (SD)          | 0           | 56.8±8.04 | 63.1 (4.80) | 59.3 (6.42) | 54.7 (7.34) | 49.9 (6.43) | <0.001* |
| Sex, n (%)              | 0           |       |     |     |     |     |         |
| Male                    | 15 782 (44.4) |       | 4362 (49.1) | 3934 (44.3) | 3784 (42.6) | 3702 (41.7) | <0.001† |
| Female                  | 19 759 (55.6) |       | 4524 (50.9) | 4951 (55.7) | 5101 (57.4) | 5183 (58.3) |         |
| Ethnicity, n (%)        | 0           |       |     |     |     |     |         |
| White                   | 33 143 (93.3) |       | 8393 (94.5) | 8343 (93.9) | 8253 (92.7) | 8172 (92.0) | <0.001† |
| Nonwhite                | 2398 (6.75) |       | 493 (5.55) | 542 (6.10) | 650 (7.32) | 713 (8.02) |         |
| Townsend index, mean (SD)| 51          | −1.09 (2.96) | −1.45 (2.79) | −1.22 (2.88) | −0.99 (3.02) | −0.70 (3.08) | <0.001* |
| Attainable education, n (%)| 0          |       |     |     |     |     |         |
| College/university or above| 12 339 (34.7) |       | 2700 (30.4) | 2946 (33.2) | 3153 (35.5) | 3540 (39.8) | <0.001† |
| Below college/university| 23 202 (65.3) |       | 6186 (69.6) | 5939 (66.8) | 5732 (64.5) | 5345 (60.2) |         |
| Smoking status, n (%)   | 177         |       |     |     |     |     |         |
| Never                   | 19 603 (55.4) |       | 4821 (54.6) | 4817 (54.5) | 4829 (54.6) | 5136 (58.1) | <0.001† |
| Former/current          | 15 761 (44.6) |       | 4013 (45.4) | 4028 (45.5) | 4015 (45.4) | 3705 (41.9) |         |
| Drinking status, n (%)  | 106         |       |     |     |     |     |         |
| Never                   | 1570 (4.43) |       | 440 (4.96) | 353 (3.98) | 391 (4.42) | 386 (4.36) | 0.018† |
| Former/current          | 33 865 (95.6) |       | 8425 (95.0) | 8517 (96.0) | 8465 (95.6) | 8458 (95.6) |         |
| Meeting physical activity recommendation, n (%) | 2441 |       |     |     |     |     |         |
| No                      | 5257 (18.1) |       | 1117 (15.6) | 1268 (17.5) | 1368 (18.8) | 1504 (20.2) | <0.001† |
| Yes                     | 23 843 (81.9) |       | 6039 (84.4) | 5977 (82.5) | 5901 (81.2) | 5926 (79.8) |         |
| Heath status, n (%)     | 194         |       |     |     |     |     |         |
| Excellent/good          | 24 579 (69.5) |       | 6402 (72.3) | 6245 (70.5) | 6091 (69.0) | 5841 (66.3) | <0.001† |
| Fair/poor               | 10 768 (30.5) |       | 2449 (27.7) | 2609 (29.5) | 2739 (31.0) | 2971 (33.7) |         |
| History of cardiovascular diseases, n (%) | 670 |       |     |     |     |     |         |
| No                      | 33 463 (96.0) |       | 8142 (94.1) | 8333 (95.8) | 8433 (96.4) | 8555 (97.5) | <0.001† |
| Yes                     | 1408 (4.04) |       | 512 (5.92) | 363 (4.17) | 314 (3.59) | 219 (2.50) |         |
| Metabolic syndrome, n (%)| 0          |       |     |     |     |     |         |
| No                      | 27 668 (77.9) |       | 6789 (76.4) | 6860 (77.2) | 6947 (78.2) | 7072 (79.6) | <0.001† |
| Yes                     | 7873 (22.1) |       | 2097 (23.6) | 2025 (22.8) | 1938 (21.8) | 1813 (20.4) |         |

*ANOVA test.
†Chi-squared test.
A total of 34,492 participants had no history of CVD events at baseline and were included for analysis. The median duration of follow-up was 5.83 years (interquartile range: 5.73–5.97). During the follow-up period, a total of 675 (2.00%) participants had incident CVD events. After adjusting for confounders, each 1-year increase in retinal age gap predicted a 3% increase in the risk of incident CVD (hazard ratio [HR]=1.03 [95% CI, 1.00–1.05]; \( P \)=0.019). This independent predictive value remained significant when ASI was incorporated into the fully adjusted model (HR=1.03 [95% CI, 1.01–1.06]; \( P \)=0.014). Compared with participants with retinal age gaps in the first quartile, those with retinal age gaps in the second (HR=1.08 [95% CI, 1.01–1.15]; \( P \)=0.018) and third quartiles (HR=1.16 [95% CI, 1.08–1.24]; \( P \)<0.001) had similar risks of developing incident CVD, while the risk was markedly increased in the fourth quartile (HR=1.55 [95% CI, 1.13–2.12]; \( P \)=0.006; Table 3). In the restricted cubic splines analysis, there were 4 knots in total. When retinal age gap=0 was used as reference, the risk of incident CVD increased significantly when the retinal age gap reached 1.21 (HR=1.05 [95% CI, 1.00–1.10]; \( P \)-overall<0.0001; \( P \)-nonlinear=0.0681; Figure).

### DISCUSSION

In the present study, we found that retinal age gap was significantly associated with ASI. In addition, the retinal age gap was found to be a predictor of future risk of incident CVD, independent of traditional risk factors, as well as ASI.

Our finding of the association between retinal age gap and ASI was consistent with previous studies, where strong associations between quantitatively assessed retinal abnormalities (eg, retinal arteriolar narrowing and venular widening) and ASI were demonstrated.\(^{39–42}\) As a clinical parameter, ASI is used to estimate the stiffness of blood vessels and an early indicator of atherosclerosis.\(^ {43}\) Higher ASI may indicate microcirculation dysfunction and target organ damage.\(^ {44,45}\) Moreover, previous research has demonstrated ASI is a strong predictor of future CVD events.\(^ {46}\) The consistent evidence suggested that the retinal age gap might be a novel biomarker of subclinical CVD.

In addition, retinal age gap was found to be an independent biomarker for future incident CVD events in this study. This association remained significant even after adjusting for baseline ASI. In keeping with our findings, a large number of previous studies have identified valuable information from fundus images including retinal microvascular signs (eg, narrower retinal arteriolar caliber and wider retinal venular caliber) and geometric parameters (eg, vessel tortuosity and bifurcation angle), as predictors for future CVD events and mortality.\(^ {12,14,47–57}\) Recently, with the advances in DL technologies, characteristics derived from retinal fundus images could be automatically extracted and learned with high efficiency for the prediction of CVD profiles and events.\(^ {19,21}\) Of note, the attention maps of our DL model\(^ {22}\) mainly highlighted the areas around the retinal vessels, suggesting that the vasculature and their surrounding areas were the key areas for...
identification of age. This spatial validation of the salience of the retinal vasculature in fundus photographs further enhances its role as a biomarker for the health of the systemic vasculature.

The pathophysiological mechanisms underlying our finding that CVD profiles and future events could be predicted from retinal images warrant further investigation. The similarities and interplay between the vasculature of the eye and the heart are likely to be the fundamental contributors. As one of the predominant risk factors, aging might result in similar pathological changes in the vasculature of these organs. First, excessive oxidative stress, lipid accumulation, and chronic inflammation caused by aging can consequently lead to endothelial dysfunction, which is a crucial process implicated in both the dysregulation of retinal blood flow and most CVD. Second, various age-related comorbidities such as hypertension, diabetes, and atherosclerosis, were found to be risk factors of CVD while simultaneously associated with structural vascular changes in the retina.

The current study found that retinal age gap may be a promising novel biomarker for future CVD risks with several important clinical implications. Imaging biomarkers of CVD risk is an emerging area of research. Previous studies have probed into the imaging biomarkers for atherosclerosis, such as carotid plaque burden, carotid intima-media thickness (IMT), and coronary artery calcification. Compared with the existing imaging biomarkers of CVD, retinal imaging has the advantages of being simple, fast, safe, and cost-effective, as well as provides insights into the end-organ damage of CVD, thus enabling unique and precise risk assessment. Further studies are warranted to validate the value of retinal age gap in individualized risk assessment for CVD. In addition, whether retinal age gap itself or its combination with other imaging biomarkers could add predictive values is another potential area

### Table 3. The Association Between Retinal Age Gap and Incident Cardiovascular Diseases

| Retinal age gap | Model I* | Model II† | Model III‡ |
|-----------------|---------|---------|-----------|
|                 | HR (95% CI) | P value  | HR (95% CI) | P value  | HR (95% CI) | P value  |
| Retinal age gap, per one age, y | 1.03 (1.01–1.05) | 0.008 | 1.03 (1.00–1.05) | 0.019 | 1.03 (1.01–1.06) | 0.014 |
| Quartiles of retinal age gap | | | | | |
| Q1 Reference | Reference | Reference | Reference | Reference | Reference | Reference |
| Q2 0.96 (0.79–1.17) | 0.706 | 1.04 (0.83–1.31) | 0.727 | 1.05 (0.84–1.32) | 0.654 |
| Q3 1.15 (0.92–1.45) | 0.216 | 1.10 (0.85–1.44) | 0.484 | 1.10 (0.84–1.44) | 0.472 |
| Q4 1.41 (1.07–1.86) | 0.016 | 1.54 (1.12–2.10) | 0.007 | 1.55 (1.13–2.12) | 0.006 |

HR indicates hazard ratio; and Q, quartile.

*Model I adjusted for baseline age, sex, and ethnicity.
†Model II adjusted for baseline age, sex, ethnicity, deprivation, attainable education, smoking status, drinking status, physical activity, health status, and metabolic syndrome.
‡Model III adjusted for baseline age, sex, ethnicity, deprivation, attainable education, smoking status, drinking status, physical activity, health status, and metabolic syndrome and arterial stiffness index.

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**Figure. Nonlinear association between retinal age gap and incident cardiovascular disease (CVD).**

Restricted cubic spline analyses were performed to assess the association between retinal age gap and incident CVD allowing nonlinearity. Five knots were placed at equal intervals across the distribution of the retinal age gap. Retinal age gap of zero years was used as the reference. Overall association between retinal age gap was observed ($P_{\text{overall}}<0.001$). A J-shaped curve was observed for the association between retinal age gap and incident CVD, where the association was significant only when retinal age gap exceeded 1.21 y. HR indicates hazard ratio.
for further research. Potential extra benefits could also be postulated. For example, screening for eye diseases through fundus photography is efficient, noninvasive, and cost-effective, and recommended for diabetic patients as part of annual screening programmes.\(^{67}\) The evaluation of retinal age gap by a DLA can be easily integrated into ocular screening programmes for the early detection and monitoring of CVD with enhanced cost-effectiveness. Notably, retinal age gap also provides a promising approach to improve early detection of cognitive decline and dementia. The close relationship between dementia (vascular dementia and Alzheimer disease) and vascular aging has been well documented.\(^{68,69}\) Therefore, further investigations are warranted for retinal age gap as a potential predictive biomarker for cognitive decline and dementia. Moreover, with the rapid development of portable electronic devices, retinal age gap may in the future be derived from smartphone-based retinal cameras and used as a point of care assessment of CVD risk; naturally, the use of nonstandardized image acquisition systems will require validation for its accuracy in future studies. Clinical application of retinal age gap may achieve an instant evaluation of systemic vasculature conditions and improve accessibility to CVD risk evaluation. It may also facilitate the early referral of patients with high CVD risk for prompt cardiology assessment and subsequent preventative interventions.

The strengths of the current study include a large sample size, relatively long duration of follow-up, the standardized protocol used for capturing fundus images, and adjustment for a wide range of confounding variables. Some limitations do remain. First, the UK Biobank study included participants that are relatively young and healthy, which might lead to selection bias and limit the representativeness and generalizability of the results. Second, ASI was measured using finger photoplethysmography (PPG) in the UK Biobank. Although it offers a simple measure with high reproducibility,\(^{571}\) PPG is susceptible to be affected by the elasticity of central arteries and the properties of the reflection sites, both central and peripheral.\(^{26}\) Third, the accuracy of incident CVD ascertainment in the UK Biobank required further scrutiny. Fourth, the retinal age gap was calculated based on fundus images captured at a specific time point. Dynamic changes in the aging of the retina over time may be a better predictor for the future risk of CVD. Finally, we could not exclude the possibility of residual confounding effects.

CONCLUSIONS

We found that retinal age gap generated by a DLA was positively associated with ASI and risk of future incident CVD. This study suggested that retinal age gap can be utilized as a novel biomarker for CVD risk evaluation, early detection, and monitoring. Future studies are needed to validate our findings in different populations.

ARTICLE INFORMATION

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Drs Zhu, Chen, Wang, He, and Yang participated in study concept and design. All authors performed acquisition, analysis, or interpretation. Drs Zhu and Chen performed drafting of the article. Drs Wang, Hu, Kiburg, Zhu, He, and Yang performed critical revision of the article for important intellectual content. Dr Zhu performed statistical analysis. Drs He and Yang obtained funding. Drs Zhu, Wang, He, and Yang provided administrative, technical, or material support. Drs He, Yang, and Huang performed study supervision.

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Disclosures

None.

Supplemental Material

Figure S1

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