Stroke

ORIGINAL ARTICLE

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

Zhuoting Zhu, MD, PhD*; Yifan Chen, MBBS*; Wei Wang, MD, PhD*; Yueye Wang, MD; Wenyi Hu, MBBS; Xianwen Shang, PhD; Huan Liao, MD, PhD; Danli Shi, MD; Yu Huang, MD, PhD; Jason Ha, MBBS; Zachary Tan, MBBS; Katerina V. Kiburg, MPH, PhD; Xueli Zhang, PhD; Shulin Tang, PhD; Honghua Yu, MD, PhD; Xiaohong Yang, MD, PhD; Mingguang He, MD, PhD

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 17.9 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

Correspondence to: Mingguang He, MD, PhD, Centre for Eye Research Australia, Level 7, 32 Gisborne St, Melbourne, Australia, Email mingguang.he@unimelb.edu.au or Zhuoting Zhu, MD, PhD, Centre for Eye Research Australia, Level 7, 32 Gisborne St, Melbourne, Australia, Email lisa.zhu@unimelb.edu.au
*Z. Zhu, Y. Chen, and W. Wang contributed equally.
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.122.038809.
For Sources of Funding and Disclosures, see page XXX.

Stroke is available at www.ahajournals.org/journal/str

ORIGINAL ARTICLE

Nonstandard Abbreviations and Acronyms

ASI	arterial stiffness index
CVD	cardiovascular disease
HR	hazard ratio

questionnaire-based models, and the involvement of invasive procedures.[6,8–10]

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 nonstereo 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.

CVD Ascertainment

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.[28] 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 of retinal age gap with the risk of incident CVD events. Images from the right eye were used to calculate the retinal age and were replaced by images from the left eye if not available.

The development and validation of the DL model for age prediction were described in details elsewhere.[22] Briefly, all fundus images were preprocessed and fed into a DL model using a Xception architecture. Data augmentation was performed during training using random horizontal or vertical flips. The algorithm was optimized using stochastic gradient descent. To avoid overfitting, we implemented a dropout of 0.5 and carried out early stopping when validation performance did not improve for 10 epochs. The DL model was trained and validated using 5-fold cross-validation. The performance of the DL model was calculated, including the mean absolute error (MAE) and the correlation between predicted retinal age and chronological age. We then retrieved attention maps from the DL model using guided Grad-CAM, which highlights pixels in the input image based on their contributions to the final evaluation.

The trained DL model was able to achieve a strong correlation of 0.80 (P<0.001) between predicted retinal age and chronological age, with an overall MAE of 3.55 years. The retinal age gap was defined as the difference between the retinal age predicted by the DL model and the chronological age. The retinal age gap would be positive for an older appearing retina compared with chronological age, while a younger appearing retina would have a negative retinal age gap.

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).[30–35] We further adjusted for ASI in the analysis of the association between retinal age gap and incident CVD.[36,37] According to the National Cholesterol Education Program adult treatment panel III guidelines (NCEP ATP III),[38] 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 covariables' variance inflation factor were <2 (mean: 1.16). A 2-sided P of <0.05 indicated statistical significance. Analyses were performed using Stata (version 13, StataCorp, TX).

ORIGINAL ARTICLE

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)		Retinal age gap				*P* value
		Total	Q1	Q2	Q3	Q4	
N		35 541	8886	8885	8885	8885	…
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)	0.016†
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)	

Q indicates quartile.
*ANOVA test.
†Chi-squared test.

Table 2. β Coefficients and OR for the Association Between Retinal Age Gap and Arterial Stiffness Index

	Linear regression		Logistic regression	
Retinal age gap	β coefficients (95% CI)	*P* value	OR (95% CI)	*P* value
Model I*				
Retinal age gap, per one age, y	0.002 (0.001–0.002)	<0.001	1.01 (1.01–1.02)	<0.001
Quartiles of retinal age gap				
Q1	Reference	Reference	Reference	Reference
Q2	0.013 (0.003–0.022)	0.008	1.08 (1.01–1.15)	0.016
Q3	0.021 (0.010–0.031)	<0.001	1.16 (1.08–1.24)	<0.001
Q4	0.018 (0.006–0.029)	0.002	1.15 (1.07–1.24)	<0.001
Model II†				
Retinal age gap, per one age, y	0.002 (0.001–0.003)	0.001	1.01 (1.01–1.02)	<0.001
Quartiles of retinal age gap				
Q1	Reference	Reference	Reference	Reference
Q2	0.013 (0.002–0.023)	0.018	1.07 (1.00–1.15)	0.050
Q3	0.018 (0.007–0.029)	0.002	1.16 (1.07–1.25)	<0.001
Q4	0.017 (0.004–0.030)	0.009	1.16 (1.06–1.26)	0.001

OR indicates odds 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, history of cardiovascular diseases, and metabolic syndrome.

Retinal Age Gap and Incident CVD

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=1.05 [95% CI, 0.84–1.32]; *P*=0.654) and third quartiles (HR=1.10 [95% CI, 0.84–1.44]; *P*=0.472) had similar risks of developing incident CVD, while the risk was markedly increased in the fourth quantile (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

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

	Model I*		Model II†		Model III‡	
Retinal age gap	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
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)	0.464	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.

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.[58] As one of the predominant risk factors, aging might result in similar pathological changes in the vasculature of these 2 organs. First, excessive oxidative stress, lipid accumulation, and chronic inflammation caused by ageing can consequently lead to endothelial dysfunction, which is a crucial process implicated in both the dysregulation of retinal blood flow and most CVD.[59,60] 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.[58,61]

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,[62–64] carotid intima-media thickness (IMT),[65] and coronary artery calcification.[66] 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

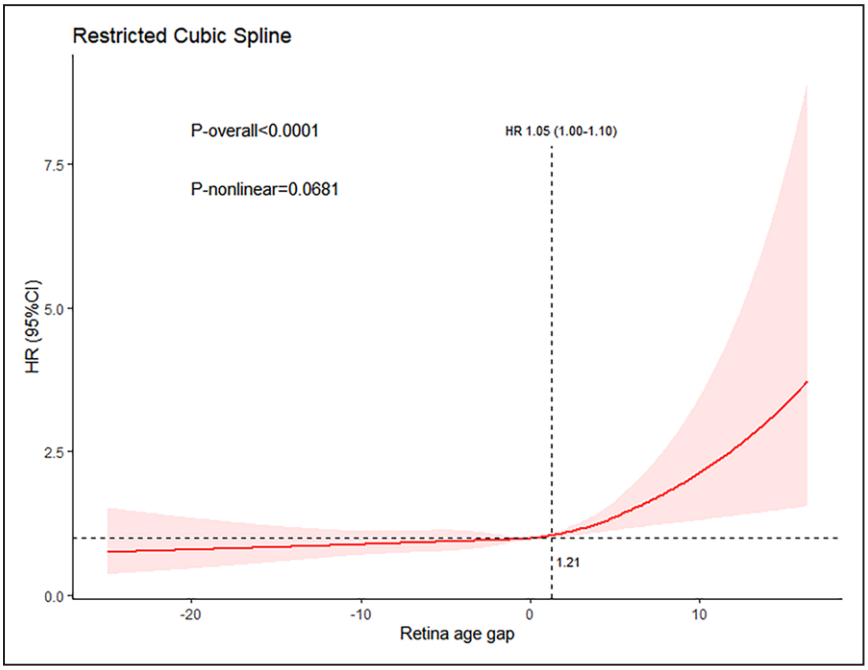

Figure. Nonlinear association between retinal age gap and incident cardiovascular disease (CVD). Restricted cubic spline analyses were performed to assess the association between retinal age gap and incident CVD allowing nonlinearity. Five knots were placed at equal intervals across the distribution of the retinal age gap. Retinal age gap of zero years was used as the reference. Overall association between retinal age gap was observed ($P_{overall}$<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.

potential area 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's 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,[70,71] PPG is susceptible to be affected by the elasticity of central arteries and the properties of the reflection sites, both central and peripheral.[25] 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

Received January 29, 2022; final revision received May 16, 2022; accepted June 13, 2022.

Affiliations

Department of Ophthalmology, Guangdong Academy of Medical Sciences, Guangdong Provincial People's Hospital, Guangzhou, China (Z.Z., X.S., Y.H., X.Z., S.T., H.Y., X.Y., M.H.). Department of Ophthalmology, Centre for Eye Research Australia, University of Melbourne, Australia (Z.Z., W.H., J.H., Z.T., K.V.K., M.H.). Ophthalmology, Department of Surgery, University of Melbourne, Australia (Z.Z., W.H., M.H.). John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, United Kingdom (Y.C.). State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China (W.W., Y.W., D.S., M.H.). Neural Regeneration Group, Institute of Reconstructive Neurobiology, University of Bonn, Germany (H.L.).

Acknowledgments

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.

Sources of Funding

The present work was supported by Fundamental Research Funds of the State Key Laboratory of Ophthalmology, National Natural Science Foundation of China (82000901, 82101173, 81870663, 82171075), NHMRC Investigator Grants (2010072), Outstanding Young Talent Trainee Program of Guangdong Provincial People's Hospital (KJ012019087), Guangdong Provincial People's Hospital Scientific Research Funds for Leading Medical Talents and Distinguished Young Scholars in Guangdong Province (KJ012019457), Talent Introduction Fund of Guangdong Provincial People's Hospital (Y012018145), Science and Technology Program of Guangzhou, China (202002020049), Project of Special Research on Cardiovascular Diseases (2020XXG007), and Research Foundation of Medical Science and Technology of Guangdong Province (B2021237). Dr He receives support from the University of Melbourne at Research Accelerator Program and the CERA Foundation. The Centre for Eye Research Australia receives Operational Infrastructure Support from the Victorian State Government. The sponsor or funding organization had no role in the design or conduct of this research.

Disclosures

None.

Supplemental Material

Figure S1

REFERENCES

1. Mortality GBD, Causes of Death C. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388:1459–1544. doi: 10.1016/S0140-6736(16)31012-1
2. Joseph P, Leong D, McKee M, Anand SS, Schwalm JD, Teo K, Mente A, Yusuf S. Reducing the Global Burden of Cardiovascular Disease, Part 1: The Epidemiology and Risk Factors. *Circ Res*. 2017;121:677–694. doi: 10.1161/CIRCRESAHA.117.308903
3. Leong DP, Joseph PG, McKee M, Anand SS, Teo KK, Schwalm JD, Yusuf S. Reducing the Global Burden of Cardiovascular Disease, Part 2: Prevention and Treatment of Cardiovascular Disease. *Circ Res*. 2017;121:695–710. doi: 10.1161/CIRCRESAHA.117.311849
4. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837–1847. doi: 10.1161/01.cir.97.18.1837

5. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Keil U, et al; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24:987–1003. doi: 10.1016/s0195-668x(03)00114-3
6. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. *BMJ*. 2007;335:136. doi: 10.1136/bmj.39261.471806.55
7. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, Dallongeville J, De Backer G, Ebrahim S, Gjelsvik B, et al; European Society of Cardiology (ESC) Committee for Practice Guidelines (CPG). European guidelines on cardiovascular disease prevention in clinical practice: executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). *Eur Heart J*. 2007;28:2375–2414. doi: 10.1093/eurheartj/ehm316
8. Hira RS, Kennedy K, Nambi V, Jneid H, Alam M, Basra SS, Ho PM, Deswal A, Ballantyne CM, Petersen LA, et al. Frequency and practice-level variation in inappropriate aspirin use for the primary prevention of cardiovascular disease: insights from the National Cardiovascular Disease Registry's Practice Innovation and Clinical Excellence registry. *J Am Coll Cardiol*. 2015;65:111–121. doi: 10.1016/j.jacc.2014.10.035
9. Brindle P, Emberson J, Lampe F, Walker M, Whincup P, Fahey T, Ebrahim S. Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. *BMJ*. 2003;327:1267. doi: 10.1136/bmj.327.7426.1267
10. González I, Pascual JC, Corona D, Hispán P, Betlloch I. European Heart Systemic Coronary Risk Evaluation may underestimate cardiovascular risk after assessing cardiovascular disease with carotid ultrasound in hidradenitis suppurativa. *Br J Dermatol*. 2018;178:e22–e23. doi: 10.1111/bjd.15776
11. Ho H, Cheung CY, Sabanayagam C, Yip W, Ikram MK, Ong PG, Mitchell P, Chow KY, Cheng CY, Tai ES, et al. Retinopathy Signs Improved Prediction and Reclassification of Cardiovascular Disease Risk in Diabetes: A prospective cohort study. *Sci Rep*. 2017;7:41492. doi: 10.1038/srep41492
12. Liew G, Wang JJ, Mitchell P, Wong TY. Retinal vascular imaging: a new tool in microvascular disease research. *Circ Cardiovasc Imaging*. 2008;1:156–161. doi: 10.1161/CIRCIMAGING.108.784876
13. Ting DSW, Peng L, Varadarajan AV & Liu TYA. Novel Retinal Imaging in Assessment of Cardiovascular Risk Factors and Systemic Vascular Diseases. in *Frontiers in Diabetes* (eds. Sabanayagam C & Wong, TY) vol. 27 106–118 (S. Karger AG, 2019).
14. McGeechan K, Liew G, Macaskill P, Irwig L, Klein R, Klein BE, Wang JJ, Mitchell P, Vingerling JR, Dejong PT, et al. Meta-analysis: retinal vessel caliber and risk for coronary heart disease. *Ann Intern Med*. 2009;151:404–413. doi: 10.7326/0003-4819-151-6-200909150-00005
15. Ding J, Wai KL, McGeechan K, Ikram MK, Kawasaki R, Xie J, Klein R, Klein BB, Cotch MF, Wang JJ, et al; Meta-Eye Study Group. Retinal vascular caliber and the development of hypertension: a meta-analysis of individual participant data. *J Hypertens*. 2014;32:207–215. doi: 10.1097/HJH.0b013e32836586f4
16. Wong TY, Islam FM, Klein R, Klein BE, Cotch MF, Castro C, Sharrett AR, Shahar E. Retinal vascular caliber, cardiovascular risk factors, and inflammation: the multi-ethnic study of atherosclerosis (MESA). *Invest Ophthalmol Vis Sci*. 2006;47:2341–2350. doi: 10.1167/iovs.05-1539
17. Guo S, Yin S, Tse G, Li G, Su L, Liu T. Association between caliber of retinal vessels and cardiovascular disease: a systematic review and meta-analysis. *Curr Atheroscler Rep*. 2020;22:16. doi: 10.1007/s11883-020-0834-2
18. Cheung CY, Xu D, Cheng CY, Sabanayagam C, Tham YC, Yu M, Rim TH, Chai CY, Gopinath B, Mitchell P, et al. A deep-learning system for the assessment of cardiovascular disease risk via the measurement of retinal-vessel calibre. *Nat Biomed Eng*. 2021;5:498–508. doi: 10.1038/s41551-020-00626-4
19. Poplin R, Varadarajan AV, Blumer K, Liu Y, McConnell MV, Corrado GS, Peng L, Webster DR. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. *Nat Biomed Eng*. 2018;2:158–164. doi: 10.1038/s41551-018-0195-0
20. Ting DSW, Wong TY. Eyeing cardiovascular risk factors. *Nat Biomed Eng*. 2018;2:140–141. doi: 10.1038/s41551-018-0210-5
21. Chang J, Ko A, Park SM, Choi S, Kim K, Kim SM, Yun JM, Kang U, Shin IH, Shin JY, et al. Association of cardiovascular mortality and deep learning-funduscopic atherosclerosis score derived from retinal fundus images. *Am J Ophthalmol*. 2020;217:121–130. doi: 10.1016/j.ajo.2020.03.027
22. Zhu Z, Shi D, Guankai P, Tan Z, Shang X, Hu W, Liao H, Zhang X, Huang Y, Yu H, et al. Retinal age gap as a predictive biomarker for mortality risk [published online January 18, 2022]. *Br J Ophthalmol*. 2022. doi: 10.1136/bjophthalmol-2021-319807
23. Savji N, Rockman CB, Skolnick AH, Guo Y, Adelman MA, Riles T, Berger JS. Association between advanced age and vascular disease in different arterial territories: a population database of over 3.6 million subjects. *J Am Coll Cardiol*. 2013;61:1736–1743. doi: 10.1016/j.jacc.2013.01.054
24. Driver JA, Djoussé L, Logroscino G, Gaziano JM, Kurth T. Incidence of cardiovascular disease and cancer in advanced age: prospective cohort study. *BMJ*. 2008;337:a2467. doi: 10.1136/bmj.a2467
25. Said MA, Eppinga RN, Lipsic E, Verweij N, van der Harst P. Relationship of arterial stiffness index and pulse pressure with cardiovascular disease and mortality. *J Am Heart Assoc*. 2018;7:e007621. doi: 10.1161/JAHA.117.007621
26. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12:e1001779. doi: 10.1371/journal.pmed.1001779
27. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370:1453–1457. doi: 10.1016/S0140-6736(07)61602-X
28. Fu H, Wang B, Shen J, Cui S, Xu Y, Liu J, Shao L. Evaluation of retinal image quality assessment networks in different color-spaces. In: *International Conference on Medical Image Computing and Computer-Assisted Intervention*. Springer, Cham;2019:48–56.
29. Deleted in proof.
30. Trudel X, Shipley MJ, McEniery CM, Wilkinson IB, Brunner EJ. Socioeconomic status, education, and aortic stiffness progression over 5 years: the Whitehall II prospective cohort study. *J Hypertens*. 2016;34:2038–2044. doi: 10.1097/HJH.0000000000001057
31. Charakida M, Georgiopoulos G, Dangardt F, Chiesa ST, Hughes AD, Rapala A, Davey Smith G, Lawlor D, Finer N, Deanfield JE. Early vascular damage from smoking and alcohol in teenage years: the ALSPAC study. *Eur Heart J*. 2019;40:345–353. doi: 10.1093/eurheartj/ehy524
32. Vandercappellen EJ, Henry RMA, Savelberg HHCM, van der Berg JD, Reesink KD, Schaper NC, Eussen SJPM, van Dongen MCJM, Dagnelie PC, Schram MT, et al. Association of the amount and pattern of physical activity with Arterial Stiffness: the Maastricht Study. *J Am Heart Assoc*. 2020;9:e017502. doi: 10.1161/JAHA.120.017502
33. van der Linde RM, Mavaddat N, Luben R, Brayne C, Simmons RK, Khaw KT, Kinmonth AL. Self-rated health and cardiovascular disease incidence: results from a longitudinal population-based cohort in Norfolk, UK. *PLoS One*. 2013;8:e65290. doi: 10.1371/journal.pone.0065290
34. Schillaci G, Pirro M, Vaudo G, Mannarino MR, Savarese G, Pucci G, Franklin SS, Mannarino E. Metabolic syndrome is associated with aortic stiffness in untreated essential hypertension. *Hypertension*. 2005;45:1078–1082. doi: 10.1161/01.HYP.0000165313.84007.7d
35. Lopes-Vicente WRP, Rodrigues S, Cepeda FX, Jordão CP, Costa-Hong V, Dutra-Marques ACB, Carvalho JC, Alves MJNN, Bortolotto LA, Trombetta IC. Arterial stiffness and its association with clustering of metabolic syndrome risk factors. *Diabetol Metab Syndr*. 2017;9:87. doi: 10.1186/s13098-017-0286-1
36. van Sloten TT, Schram MT, van den Hurk K, Dekker JM, Nijpels G, Henry RM, Stehouwer CD. Local stiffness of the carotid and femoral artery is associated with incident cardiovascular events and all-cause mortality: the Hoorn study. *J Am Coll Cardiol*. 2014;63:1739–1747. doi:10.1016/j.jacc.2013.12.041
37. Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, Asmar R, Reneman RS, Hoeks AP, Breteler MM, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. *Circulation*. 2006;113:657–663. doi: 10.1161/CIRCULATIONAHA.105.555235
38. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497. doi: 10.1001/jama.285.19.2486
39. Triantafyllou A, Anyfanti P, Gavriilaki E, Zabulis X, Gkaliagkousi E, Petidis K, Triantafyllou G, Gkolias V, Pyrpasopoulou A, Douma S. Association between retinal vessel caliber and arterial stiffness in a population comprised of normotensive to early-stage hypertensive individuals. *Am J Hypertens*. 2014;27:1472–1478. doi: 10.1093/ajh/hpu074

40. Tapp RJ, Owen CG, Barman SA, Welikala RA, Foster PJ, Whincup PH, Strachan DP, Rudnicka AR. Associations of retinal microvascular diameters and tortuosity with blood pressure and arterial stiffness: United Kingdom Biobank. *Hypertension*. 2019;74:1383–1390. doi: 10.1161/HYPERTENSIONAHA.119.13752
41. Liao D, Wong TY, Klein R, Jones D, Hubbard L, Sharrett AR. Relationship between carotid artery stiffness and retinal arteriolar narrowing in healthy middle-aged persons. *Stroke*. 2004;35:837–842. doi: 10.1161/01.STR.0000120310.43457.AD
42. Meyer ML, Klein BE, Klein R, Palta P, Sharrett AR, Heiss G, Nambi V, Wong TY, Tanaka H. Central arterial stiffness and retinal vessel calibers: the Atherosclerosis Risk in Communities Study-Neurocognitive Study. *J Hypertens*. 2020;38:266–273. doi: 10.1097/HJH.0000000000002252
43. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27:2588–2605. doi: 10.1093/eurheartj/ehl254
44. Vasan RS, Short MI, Niiranen TJ, Xanthakis V, DeCarli C, Cheng S, Seshadri S, Mitchell GF. Interrelations between arterial stiffness, target organ damage, and cardiovascular disease outcomes. *J Am Heart Assoc*. 2019;8:e012141. doi: 10.1161/JAHA.119.012141
45. Tsao CW, Himali JJ, Beiser AS, Larson MG, DeCarli C, Vasan RS, Mitchell GF, Seshadri S. Association of arterial stiffness with progression of subclinical brain and cognitive disease. *Neurology*. 2016;86:619–626. doi: 10.1212/WNL.0000000000002368
46. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55:1318–1327. doi: 10.1016/j.jacc.2009.10.061
47. Wong TY, Wong T, Mitchell P. The eye in hypertension. *Lancet*. 2007;369:425–435. doi: 10.1016/S0140-6736(07)60198-6
48. Wong TY, Mitchell P. Hypertensive retinopathy. *N Engl J Med*. 2004;351:2310–2317. doi: 10.1056/NEJMra032865
49. Nguyen TT, Wong TY. Retinal vascular manifestations of metabolic disorders. *Trends Endocrinol Metab*. 2006;17:262–268. doi: 10.1016/j.tem.2006.07.006
50. Grunwald JE, Ying GS, Maguire M, Pistilli M, Daniel E, Alexander J, Whittock-Martin R, Parker C, Mohler E, Lo JC, et al; Chronic Renal Insufficiency Cohort (CRIC) Study Group. Association between retinopathy and cardiovascular disease in patients with chronic kidney disease (from the Chronic Renal Insufficiency Cohort [CRIC] Study). *Am J Cardiol*. 2012;110:246–253. doi: 10.1016/j.amjcard.2012.03.014
51. Duncan BB, Wong TY, Tyroler HA, Davis CE, Fuchs FD. Hypertensive retinopathy and incident coronary heart disease in high risk men. *Br J Ophthalmol*. 2002;86:1002–1006. doi: 10.1136/bjo.86.9.1002
52. Lam A, Bunya VY, Piltz-Seymour JR. Cardiovascular risk factors and events in glaucoma patients with peripapillary focal arteriolar narrowing. *Acta Ophthalmol Scand*. 2006;84:69–73. doi: 10.1111/j.1600-0420.2005.00515.x
53. Wong TY, Klein R, Nieto FJ, Klein BE, Sharrett AR, Meuer SM, Hubbard LD, Tielsch JM. Retinal microvascular abnormalities and 10-year cardiovascular mortality: a population-based case-control study. *Ophthalmology*. 2003;110:933–940. doi: 10.1016/S0161-6420(03)00084-8
54. Witt N, Wong TY, Hughes AD, Chaturvedi N, Klein BE, Evans R, McNamara M, Thom SA, Klein R. Abnormalities of retinal microvascular structure and risk of mortality from ischemic heart disease and stroke. *Hypertension*. 2006;47:975–981. doi: 10.1161/01.HYP.0000216717.72048.6c
55. Patton N, Aslam TM, MacGillivray T, Deary IJ, Dhillon B, Eikelboom RH, Yogesan K, Constable IJ. Retinal image analysis: concepts, applications and potential. *Prog Retin Eye Res*. 2006;25:99–127. doi: 10.1016/j.preteyeres.2005.07.001
56. Allon R, Aronov M, Belkin M, Maor E, Shechter M, Fabian ID. Retinal microvascular signs as screening and prognostic factors for cardiac disease: a systematic review of current evidence. *Am J Med*. 2021;134:36–47.e7. doi: 10.1016/j.amjmed.2020.07.013
57. Liew G, Mitchell P, Rochtchina E, Wong TY, Hsu W, Lee ML, Wainwright A, Wang JJ. Fractal analysis of retinal microvasculature and coronary heart disease mortality. *Eur Heart J*. 2011;32:422–429. doi: 10.1093/eurheartj/ehq431
58. Flammer J, Konieczka K, Bruno RM, Virdis A, Flammer AJ, Taddei S. The eye and the heart. *Eur Heart J*. 2013;34:1270–1278. doi: 10.1093/eurheartj/eht023
59. El Assar M, Angulo J, Rodríguez-Mañas L. Oxidative stress and vascular inflammation in aging. *Free Radic Biol Med*. 2013;65:380–401. doi: 10.1016/j.freeradbiomed.2013.07.003
60. Tesauro M, Mauriello A, Rovella V, Annicchiarico-Petruzzelli M, Cardillo C, Melino G, Di Daniele N. Arterial ageing: from endothelial dysfunction to vascular calcification. *J Intern Med*. 2017;281:471–482. doi: 10.1111/joim.12605
61. Monteiro-Henriques I, Rocha-Sousa A, Barbosa-Breda J. Optical coherence tomography angiography changes in cardiovascular systemic diseases and risk factors: A Review. *Acta Ophthalmol*. 2022;100:e1–e15. doi: 10.1111/aos.14851
62. Spence JD, Eliasziw M, DiCicco M, Hackam DG, Galil R, Lohmann T. Carotid plaque area: a tool for targeting and evaluating vascular preventive therapy. *Stroke*. 2002;33:2916–2922. doi: 10.1161/01.str.0000042207.16156.b9
63. Spence JD, Hackam DG. Treating arteries instead of risk factors: a paradigm change in management of atherosclerosis. *Stroke*. 2010;41:1193–1199. doi: 10.1161/STROKEAHA.110.577973
64. Mathiesen EB, Bønaa KH, Joakimsen O. Echolucent plaques are associated with high risk of ischemic cerebrovascular events in carotid stenosis: the tromsø study. *Circulation*. 2001;103:2171–2175. doi: 10.1161/01.cir.103.17.2171
65. Wendelhag I, Wiklund O, Wikstrand J. On quantifying plaque size and intima-media thickness in carotid and femoral arteries. Comments on results from a prospective ultrasound study in patients with familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol*. 1996;16:843–850. doi: 10.1161/01.atv.16.7.843
66. Baber U, Mehran R, Sartori S, Schoos MM, Sillesen H, Muntendam P, Garcia MJ, Gregson J, Pocock S, Falk E, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. *J Am Coll Cardiol*. 2015;65:1065–1074. doi: 10.1016/j.jacc.2015.01.017
67. Scanlon PH. The English National Screening Programme for diabetic retinopathy 2003-2016. *Acta Diabetol*. 2017;54:515–525. doi: 10.1007/s00592-017-0974-1
68. Cortes-Canteli M, Iadecola C. Alzheimer's disease and vascular aging: JACC focus seminar. *J Am Coll Cardiol*. 2020;75:942–951. doi: 10.1016/j.jacc.2019.10.062
69. Yang T, Sun Y, Lu Z, Leak RK, Zhang F. The impact of cerebrovascular aging on vascular cognitive impairment and dementia. *Ageing Res Rev*. 2017;34:15–29. doi: 10.1016/j.arr.2016.09.007
70. Dregan A, Rayner L, Davis KAS, Bakolis I, Arias de la Torre J, Das-Munshi J, Hatch SL, Stewart R, Hotopf M. Associations between depression, arterial stiffness, and metabolic syndrome among adults in the UK Biobank population study: a mediation analysis. *JAMA Psychiatry*. 2020;77:598–606. doi: 10.1001/jamapsychiatry.2019.4712
71. Clarenbach CF, Stoewhas AC, van Gestel AJ, Latshang TD, Lo Cascio CM, Bloch KE, Kohler M. Comparison of photoplethysmographic and arterial tonometry-derived indices of arterial stiffness. *Hypertens Res*. 2012;35:228–233. doi: 10.1038/hr.2011.168