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Original Article

ORIGINAL ARTICLE

Association of retinal age gap with chronic kidney disease and subsequent cardiovascular disease sequelae: a cross-sectional and longitudinal study from the UK Biobank

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ABSTRACT

Background. Chronic kidney disease (CKD) increases the risk of cardiovascular disease (CVD) and is more prevalent in older adults. Retinal age gap, a biomarker of aging based on fundus images, has been previously developed and validated. This study aimed to investigate the association of retinal age gap with CKD and subsequent CVD complications.
Methods. A deep learning model was trained to predict the retinal age using 19 200 fundus images of 11 052 participants without any medical history at baseline. Retinal age gap, calculated as retinal age predicted minus chronological age, was calculated for the remaining 35 906 participants. Logistic regression models and Cox proportional hazards regression models were used for the association analysis.
Results. A total of 35 906 participants (56.75 ± 8.04 years, 55.68% female) were included in this study. In the cross-sectional analysis, each 1-year increase in retinal age gap was associated with a 2% increase in the risk of CKD prevalence [odds ratio 1.02, 95% confidence interval (CI) 1.01–1.04, $P = .012$]. A longitudinal analysis of 35 039 participants demonstrated that 2.87% of them developed CKD in follow-up, and each 1-year increase in retinal age gap was associated with a 3% increase in the risk of CKD incidence (hazard ratio 1.03, 95% CI 1.01–1.05, $P = .004$). In addition, a total of 111 CKD patients (15.81%) developed CVD in follow-up, and each 1-year increase in retinal age gap was associated with a 10% increase in the risk of incident CVD (hazard ratio 1.10, 95% CI 1.03–1.17, $P = .005$).
Conclusions. We found that retinal age gap was independently associated with the prevalence and incidence of CKD, and also associated with CVD complications in CKD patients. This supports the use of this novel biomarker in identifying individuals at high risk of CKD and CKD patients with increased risk of CVD.

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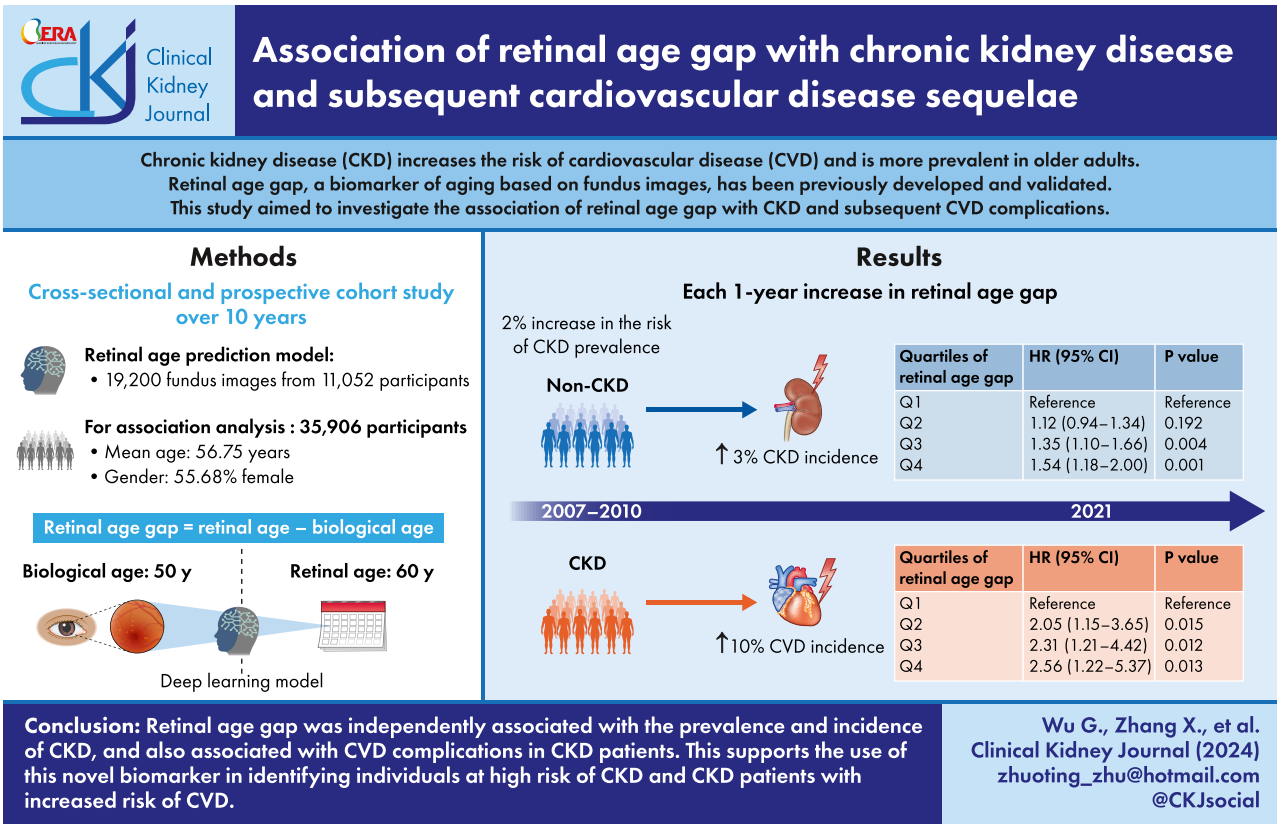
GRAPHICAL ABSTRACT



Keywords: ageing, biomarkers, cardiovascular diseases, chronic kidney disease

KEY LEARNING POINTS

What was known:

- Quantifying the aging process has great clinical significance in risk stratification and the implementation of early intervention for chronic kidney disease (CKD) and its cardiovascular disease (CVD) complications.
- However, the clinical application of aging biomarkers associated with CKD or CVD has been challenging due to invasive, expensive or time-consuming disadvantages.

This study adds:

- In this study, we found that retinal age gap (the difference between the predicted age based on fundus images and actual age), a clinically validated biomarker of aging, was independently associated with the prevalence and incidence of CKD, and also associated with CVD complications in CKD patients.
- Thus, retinal age gap may be a promising noninvasive predictive biomarker for incident CKD along with its CVD complications.

Potential impact:

- As an aging biomarker, retinal age gap has great potential in identifying individuals at high risk for CKD and its CVD complications, thus allowing for personalized prevention and management of CKD along with its CVD complications.

INTRODUCTION

Chronic kidney disease (CKD) is a chronic progressive condition affecting over 800 million people globally [1, 2]. Cardiovascular diseases (CVD) is currently the leading cause of death in CKD patients, with many CKD patients dying due to CVD complications before progressing to end-stage renal disease [3]. Therefore, early detection, intervention of CKD and CVD complications are crucial for improving patient outcomes.

Aging is a well-known major risk factor for both CKD and CVD [4–6]. Quantifying the aging process has great clinical significance in risk stratification and the implementation of

early intervention for CKD and its CVD complications. While chronological age reflects aging to some extent, individuals with the same chronological age and similar clinical profiles often show stark differences in age-related kidney and cardiovascular health impairments [7]. Biological age is a more accurate indicator to quantify the degree of aging and reflect the health status of the body. Thus, biological age could have more value than chronological age in the prediction of age-related diseases and mortality [8]. Previously, cellular and molecular aging biomarkers, such as telomere length [9, 10], epigenetic changes [11, 12] and inflammatory/immune features [13], have been described to be associated with CKD or kidney function decline, although the acquisition of these markers is invasive, expensive or time-consuming, which creates challenges for large-scale early screening and risk management of CKD. In recent years, the rapid development of deep learning (DL) technology has provided a new means to assess biological age [14]. However, there is still a considerable gap in applying image-based aging biomarkers to CKD assessment. Moreover, CKD patients are at high risk of incident CVD. As CKD progresses, associations of traditional risk factors such as body mass index (BMI), lipids and blood pressure with CVD outcomes are attenuated or reversed, reducing the predictive power, and other risk factors such as aging biomarkers may become more important [15]. It remains unclear whether aging biomarkers associated with CKD can be used to predict incidence of CVD complications in patients with CKD.

The retina is a non-invasive window for evaluating the systemic microcirculation and overall health status, with potential to measure biological aging [16, 17]. Therefore, we use a DL model to predict the actual age of healthy individuals based on fundus images. We found that retinal age gap, calculated as the difference between the predicted age (retinal age) and actual age, was associated with mortality, suggesting a new aging biomarker [18]. In addition, we have demonstrated the prediction value in the general population of retinal age gap for systemic diseases and indices including Parkinson's disease, metabolic syndrome, stroke and CVD, as well as cardiovascular health metrics [19–23]. Currently, it is unknown whether the retinal age gap can identify and predict early-stage CKD, as well as predict the risk of future CVD, in CKD patients.

Therefore, the purpose of this study is to explore the association between the retinal age gap and the prevalence and incidence of CKD using the UK Biobank, as well as further investigate the association between the retinal age gap and future CVD among CKD patients.

MATERIALS AND METHODS

Study population

The UK Biobank is a national, prospective, population-based database including more than 500 000 participants aged 40–69 years throughout the UK between 2006 and 2010 (http://www.ukbiobank.ac.uk). Participants provided extensive health-related information through questionnaires, interviews, physical measurements, biological sample collection and imaging at one of 22 assessment centers across England, Scotland and Wales. The design, method, and population of the UK Biobank study have been previously detailed elsewhere [24].

The North West Multicentre Research Ethics Committee (21/NW/0157; 29 June 2021) granted the UK Biobank study's ethical approval. UK Biobank provided all data analyzed herein under project reference and data transfer agreement number 86091. The study adhered to the tenets of the Declarations of the Helsinki. Written informed consent was obtained from all participants.

Ophthalmic measures

Comprehensive ophthalmic examinations were conducted in 2010 at six assessment centers. This included the logarithm of the minimum angle of resolution (LogMAR) visual acuity, autorefraction and keratometry (Tomey RC5000, Tomey GmbH, Nuremberg, Germany), intraocular pressure (Ocular Response Analyzer, Reichert, Buffalo, NY, USA), and paired fundus photographs and optical coherence tomography (Topcon 3D OCT 1000 Mk2, Topcon Corp., Tokyo, Japan). Fundus photographs for each eye were obtained from 45° non-mydriatic and non-stereo fundus images of both optic disc- and macular-centered. We downloaded 131 238 fundus images from 66 500 participants in the UK Biobank study. After image quality control, a total of 80 169 images from 46 958 participants were available for subsequent analysis. The image quality check process has been described in details elsewhere [18].

DL model for age prediction

We selected 19 200 fundus images of disease-free participants (11 052 individuals) from 80 169 images for developing a DL model to predict age. To maximize the available data, we used images from both eyes in model training. Details of the methods and performance of the DL model can be found in our previous study [18]. In brief, the DL model had a high accuracy in predicting retinal age, with a correlation coefficient of 0.81 ($P < .001$) between retinal age and chronological age and an overall mean absolute error of 3.55 years. Using this DL model, we estimated the retinal age of the remaining participants (35 906) with fundus images. As they were from the general population, we did not exclude participants with retinal disease. The remaining 35 906 participants were used to investigate the cross-sectional and longitudinal associations between retinal age gap and CKD, as well as the potential association between retinal age gap and incident CVD complications in patients with CKD. We used right-eye images for predicting retinal age, and left-eye images when right-eye images were unavailable.

Definition of retinal age gap

We defined retinal age gap as the difference between the predicted retinal age by the DL model and chronological age. When the retinal age gap is positive, the patient's retina has a more advanced aging state than their chronological age, while a negative retinal age gap means a younger state than the chronological age. The distribution of retinal age gap was shown in Supplementary data, Fig. S1.

Ascertainment of CKD and CVD cases

There were three outcomes of interest: baseline prevalence of CKD cases, incidence of CKD and incidence of CVD. Prevalence CKD case in the UK Biobank study were determined by combining data from an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 at the time of recruitment, participants' medical histories, and record linkage to hospital admissions data, the national death register and data of operations and procedures performed during hospital inpatient admissions. Hospital admissions data and the national death register data used the International Classification of Diseases (ICD) codes,

and data of operations and procedures during admissions used the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, version 4 (OPCS4) codes. Incident CKD cases were identified using ICD codes in hospital inpatient data, death register records and OPCS4 codes in operations and procedures during admissions. In addition, incidence of CVD was defined as the first occurrence of myocardial infarction, heart failure, venous thromboembolism or stroke during follow-up using ICD codes from hospital admissions data and the national death register. The diagnosis codes of CKD and CVD are detailed in Supplementary data, Table S1.

Covariates

Covariables in the analysis included age, sex, ethnicity, education (college degree/others/unknown), Townsend deprivation index, smoking status (never/former/current/missing), drinking status (never/former/current/missing), physical activity (low/moderate/high level/missing), obesity (no/yes), comorbidities (diabetes, hypertension and CVD), eGFR, cholesterol, vitamin D and C-reactive protein. Sociodemographic and lifestyle factors were self-reported. Physical parameters and blood indicators were objectively measured. Obesity was defined as a BMI of 30 kg/m^2 or more. eGFR was assessed by measuring serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation [25]. Diabetes was defined as HbA1c >6.5%, taking anti-hyperglycemic medications or using insulin, or prevalence self-reported. Hypertension was considered a systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg averaged over two measurements, taking antihypertensive drugs or prevalence self-reported.

Statistical analysis

Baseline characteristics were summarized as a percentage for categorical variables and means ± standard deviations (SDs) for continuous variables. We compared the characteristics of participants between two groups using the Chi-square test for categorical variables and the independent t-test for continuous variables.

Retinal age gap was introduced into the models as a continuous variable (per 1-year increase) and a categorical variable, respectively. In the cross-sectional analysis of prevalent CKD, we categorized the retinal age gap into seven equal parts. Specifically, P1, P2 and P3 each included two of these parts, while P4 only included the last part. Consequently, we used the categories P1 to P4 as the categorical variable for the retinal age gap in our analysis. This categorization aimed to ensure that the relationship between the retinal age gap and the prevalence of CKD was not obscured. In the analysis of incident CKD and CVD complication, we used quartiles (Q1–Q4) as the categorical variable for the retinal age gap. First, multivariable logistic regression models were used to assess the association between retinal age gap and CKD prevalence. We adjusted logistic regression models for the following covariates: age, gender and ethnicity (Model 1); education, Townsend index, smoking status, drinking status, physical activity, obesity, cholesterol, vitamin D, C-reactive protein, history of diabetes, history of hypertension and history of CVD (Model 2); and the age-squared term (Model 3). Second, multivariable Cox proportional hazards regression models were used to investigate the association of retinal age gap with CKD incidence, and CKD patients' future CVD. We adjusted Cox models for the following covariates: age, gender and ethnicity (Model 1); education, Townsend index, smoking status, drinking status, physical activity, obesity, eGFR, cholesterol, Vitamin D, C-reactive protein, history of diabetes, history of hypertension and history of CVD (adjusted only in CKD analysis) (Model 2); and the age-squared term (Model 3). Besides, we assessed the non-linear relationship between the retinal age gap with CKD prevalence, CKD incidence and CKD patients' incidence of CVD using restricted cubic spline analysis. Four knots were placed at equal intervals across the distribution of the retinal age gap. Retinal age gap of 0 years was used as the reference. Moreover, we excluded patients who had CKD and CVD in 2 years of follow-up, respectively, for sensitivity analyses. We also assessed potential interaction with diabetes, hypertension, and baseline eGFR regarding the association between retinal age gap and CKD-related outcomes.

Logistic regression models were used to evaluate the predictive value of retinal age and reported prediction equations for CVD in CKD patients. The prediction equations in this analysis included the Pooled Cohort Equations (PCEs) (age, gender, ethnicity, smoking status, cholesterol, high-density lipoprotein, systolic blood pressure, use of blood pressure-lowering medications and history of diabetes) and the Chronic Renal Insufficiency Cohort (CRIC) equation (age, smoking status, cholesterol, high-density lipoprotein, systolic blood pressure, urinary albumin-to-creatinine ratio, glycosylated hemoglobin and hemoglobin) [26, 27]. The area under the receiver operator characteristic curves (AUC) was used to estimate the discrimination.

All statistical analyses were performed using Stata version 16.0 (StataCorp, College Station, TX, USA) and R (version 3.3.0, R Foundation for Statistical Computing, www.R-project.org, Vienna, Austria). Double-sided *P*-value <.05 was considered statistically significant.

RESULTS

Population characteristics

Among 502 386 participants, 455 428 were excluded due to missing or poor-quality retinal images (Fig. 1), resulting in a final cohort of 35906 participants (55.68% women) aged 40–70 years (mean ± SD 56.75 ± 8.04). At baseline, 867 participants (2.41%) had CKD and 35 039 participants (97.59%) did not have CKD. Participants with and without CKD were stratified into four groups based on quartiles of retinal age gap, with baseline characteristics detailed in Table 1. Individuals with a higher retinal age gap exhibit several characteristics, including younger age, lower levels of vitamin D, being female, obesity, college degree and having a larger Townsend index. Intuitively, among participants without CKD, individuals with a great retinal age gap had higher eGFR levels at baseline and were less likely to have hypertension and CVD.

Association of retinal age gap with CKD prevalence

In the cross-sectional analysis (Table 2), we found each 1-year increase in retinal age gap was associated with a 2% increase in the risk of CKD prevalence [odds ratio (OR) 1.02, 95% confidence interval (CI) 1.01–1.04, $P = .012$] after possible confounders had been adjusted. Compared with participants with retinal age gap in P1, participants with retinal age gap in P2 and P3 had similar risks of CKD prevalence, while those with retinal age gap in P4 had a 1.69-fold increased risk (OR 1.69, 95% CI 1.19–2.41, $P = .003$). Overall association between retinal age gap and CKD prevalence was observed in the restricted cubic splines analysis

Table 1: Baseline characteristics of the study participants stratified by quantiles of retinal age gap.

	No-CKD participants (for analysis of incident CKD)					CKD participants (for analysis of incident CVD)				
		Retinal age gap					Retinal age gap			
Baseline characteristics	Total	Q1	Q2	Q3	Q4	Total	Q1	Q2	Q3	Q4
N	35 039	8760	8760	8760	8759	702	176	175	176	175
Age, years	56.61 ± 8.04	63.01 ± 4.83	59.12 ± 6.46	54.53 ± 7.32	49.76 ± 6.41	62.60 ± 5.74	65.85 ± 3.47	64.79 ± 3.85	62.23 ± 4.72	57.51 ± 6.45
Gender										
Female	19 504 (55.66)	4461 (50.92)	4877 (55.67)	5063 (57.80)	5103 (58.26)	430 (61.25)	99 (56.25)	98 (56.00)	121 (68.75)	112 (64.00)
Male	15 535 (44.34)	4299 (49.08)	3883 (44.33)	3697 (42.20)	3656 (41.74)	272 (38.75)	77 (43.75)	77 (44.00)	55 (31.25)	63 (36.00)
Ethnicity										
Whites	32 653 (93.19)	8267 (94.37)	8219 (93.82)	8103 (92.50)	8064 (92.07)	660 (94.02)	167 (94.89)	164 (93.71)	167 (94.89)	162 (92.57)
Non-whites	2191 (6.25)	447 (5.10)	504 (5.75)	605 (6.91)	635 (7.25)	36 (5.13)	7 (3.98)	10 (5.71)	9 (5.11)	10 (5.71)
Unknown	195 (0.56)	46 (0.53)	37 (0.42)	52 (0.59)	60 (0.69)	6 (0.85)	2 (1.14)	1 (0.57)	0 (0.00)	3 (1.71)
Townsend index	−1.09 ± 2.95	−1.46 ± 2.79	−1.22 ± 2.88	−1.01 ± 3.02	−0.69 ± 3.08	−0.99 ± 2.96	−1.35 ± 3.09	−1.20 ± 2.82	−1.06 ± 2.79	−0.32 ± 3.04
Education level										
College degree	12 223 (34.88)	2685 (30.65)	2943 (33.60)	3117 (35.58)	3478 (39.71)	208 (29.63)	51 (28.98)	44 (25.14)	53 (30.11)	60 (34.29)
Others	22 424 (64.00)	5968 (68.13)	5746 (65.59)	5543 (63.28)	5167 (58.99)	483 (68.80)	121 (68.75)	128 (73.14)	121 (68.75)	113 (64.57)
Unknown	392 (1.12)	107 (1.22)	71 (0.81)	100 (1.14)	114 (1.30)	11 (1.57)	4 (2.27)	3 (1.71)	2 (1.14)	2 (1.14)
Obesity										
No	26 056 (74.74)	6665 (76.50)	6521 (74.77)	6504 (74.77)	6366 (73.05)	450 (64.47)	120 (68.57)	109 (63.01)	119 (68.00)	102 (58.29)
Yes	8806 (25.26)	2047 (23.50)	2200 (25.23)	2211 (25.37)	2348 (26.95)	248 (35.53)	55 (31.43)	64 (36.99)	56 (32.00)	73 (41.71)
Smoking status										
Never	19 326 (55.16)	4748 (54.20)	4758 (54.32)	4792 (54.70)	5028 (57.40)	400 (56.98)	100 (56.82)	97 (55.43)	103 (58.52)	100 (57.14)
Former	12 306 (35.13)	3376 (38.54)	3242 (37.01)	3019 (34.46)	2672 (30.51)	261 (37.18)	66 (37.50)	69 (39.43)	67 (38.07)	59 (33.71)
Current	3227 (9.21)	585 (6.68)	719 (8.21)	906 (10.34)	1017 (11.61)	38 (5.41)	8 (4.55)	8 (4.57)	6 (3.41)	16 (9.14)
Missing	177 (0.51)	51 (0.58)	41 (0.47)	43 (0.49)	42 (0.48)	3 (0.43)	2 (1.14)	1 (0.57)	0 (0.00)	0 (0.00)
Drinking status										
Never	1523 (4.35)	417 (4.76)	353 (4.03)	381 (4.35)	372 (4.25)	54 (7.69)	20 (11.36)	11 (6.29)	12 (6.82)	11 (6.29)
Former	1347 (3.84)	312 (3.56)	345 (3.94)	328 (3.74)	362 (4.13)	29 (4.13)	3 (1.70)	7 (4.00)	7 (3.98)	12 (6.86)
Current	32 062 (91.50)	8012 (91.46)	8046 (91.85)	8021 (91.56)	7983 (91.14)	617 (87.79)	151 (85.50)	157 (89.71)	157 (89.20)	152 (86.86)
Missing	107 (0.31)	19 (0.22)	16 (0.18)	30 (0.34)	42 (0.48)	2 (0.28)	2 (1.14)	0 (0.00)	0 (0.00)	0 (0.00)
Physical activity										
Low	5240 (14.95)	1172 (13.38)	1236 (14.11)	1388 (15.84)	1446 (16.51)	102 (14.53)	28 (15.91)	22 (12.57)	21 (11.93)	31 (17.71)
Moderate	11 939 (34.07)	2943 (33.60)	3025 (34.53)	2987 (34.10)	2984 (34.07)	234 (33.33)	60 (34.09)	63 (36.00)	54 (30.68)	57 (32.57)
High	11 539 (32.93)	2969 (33.89)	2878 (32.85)	2822 (32.21)	2870 (34.77)	210 (29.91)	45 (25.57)	56 (32.00)	50 (28.41)	59 (33.71)
Missing	6319 (18.03)	1676 (19.13)	1621 (18.50)	1563 (17.84)	1459 (16.66)	256 (22.22)	43 (24.43)	34 (19.43)	51 (28.98)	28 (16.00)
eGFR, mL/min/1.73 m^2	90.36 ± 11.96	85.75 ± 10.57	88.25 ± 11.11	91.84 ± 11.87	95.58 ± 11.89	53.55 ± 11.15	53.57 ± 8.27	53.19 ± 11.60	53.18 ± 9.69	54.29 ± 14.27
Cholesterol, mmol/L	5.67 ± 1.14	5.66 ± 1.19	5.73 ± 1.14	5.70 ± 1.13	5.59 ± 1.10	5.38 ± 1.18	5.32 ± 1.17	5.45 ± 1.23	5.45 ± 1.17	5.30 ± 1.13
Vitamin D, nmol/L	45.84 ± 20.37	48.78 ± 20.42	47.01 ± 20.20	44.55 ± 20.23	43.06 ± 20.15	49.97 ± 22.17	52.38 ± 21.62	50.64 ± 22.37	50.20 ± 22.03	46.58 ± 22.46
C-reactive protein, mg/L	2.54 ± 4.27	2.51 ± 4.07	2.47 ± 3.98	2.59 ± 4.64	2.57 ± 4.34	3.56 ± 5.55	3.08 ± 3.31	4.31 ± 7.23	3.67 ± 6.73	3.17 ± 3.77
History of diabetes	2221 (6.34)	543 (6.20)	569 (6.50)	521 (5.95)	588 (6.71)	90 (12.82)	18 (10.23)	18 (10.29)	28 (15.91)	26 (14.86)
History of hypertension	26 421 (75.40)	7238 (82.63)	6848 (78.17)	6402 (73.08)	5933 (67.74)	613 (87.32)	160 (90.91)	144 (82.29)	155 (88.07)	154 (88.00)
History of CVD	2335 (6.66)	773 (8.82)	632 (7.21)	508 (5.80)	422 (4.82)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Data are presented as mean ± SD, or *N* (%).

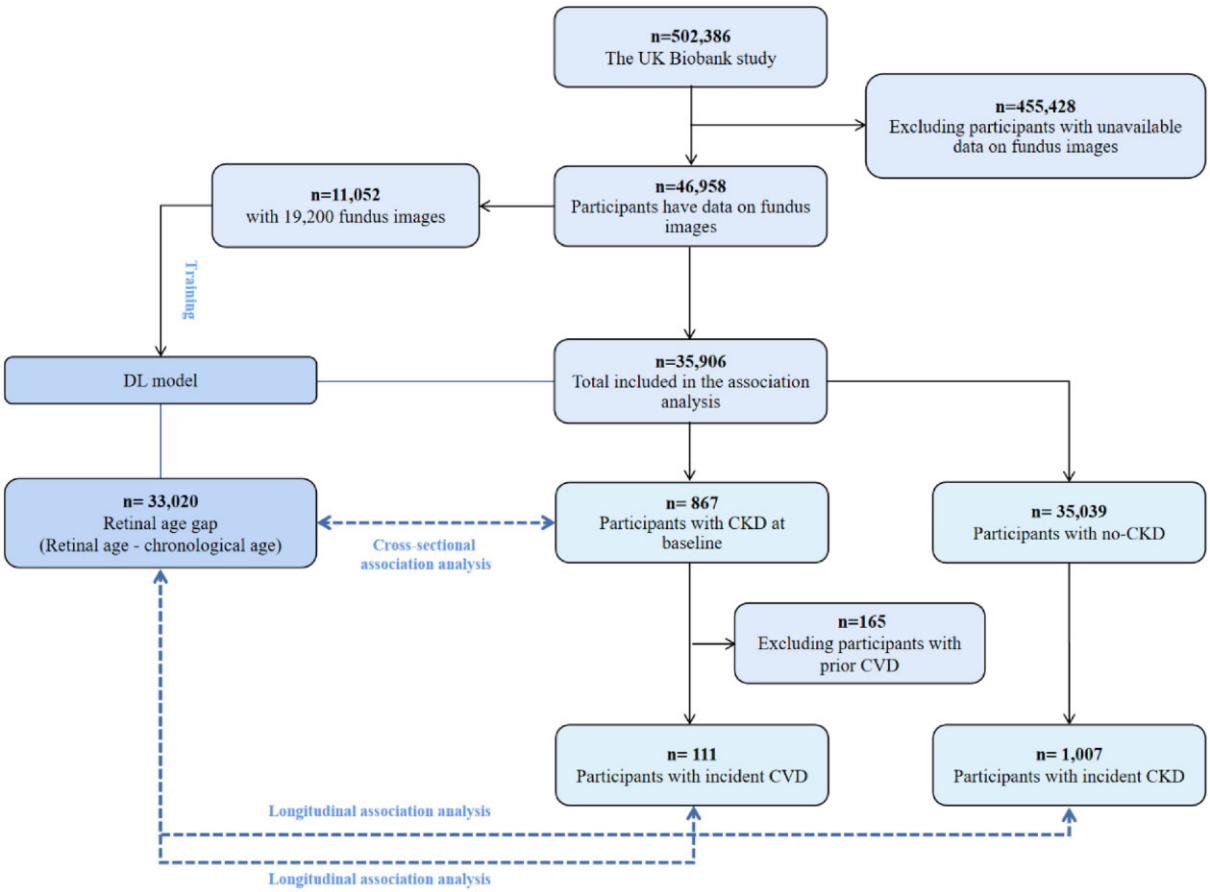


Figure 1: Flow chart of data analysis.

Table 2: Association between retinal age gap and CKD prevalence.

		Model 1[a]		Model 2[b]		Model 3[c]	
Retinal age gap	Total	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Retinal age gap, per one age (year)	35 906	1.03 (1.01–1.05)	**.003**	1.02 (1.00–1.04)	**.018**	1.02 (1.01–1.04)	**.012**
Retinal age gap category							
P1	10 259	Reference		Reference		Reference	
P2	10 259	1.13 (0.96–1.33)	.142	1.12 (0.94–1.32)	.203	1.13 (0.95–1.34)	.180
P3	10 259	1.22 (0.98–1.51)	.072	1.13 (0.90–1.41)	.297	1.14 (0.91–1.44)	.265
P4	5129	1.90 (1.36–2.65)	**<.001**	1.70 (1.19–2.41)	**.003**	1.69 (1.19–2.41)	**.003**

P1 is defined as the set of data between the smallest value and the 28th retinal age gap. The P2 is the set of data between the 28th and 57th retinal age gap. The P3 is set of data between the 57th and the 85th retinal age gap. The P4 is defined as the set of data between the 85th and the maximum of the retinal age gap.
[a]Model 1 adjusted for age, gender and ethnicity.
[b]Model 2 adjusted for age, gender, ethnicity, education, Townsend index, smoking status, drinking status, physical activity, obesity, cholesterol, vitamin D, C-reactive protein, history of diabetes, history of hypertension and history of CVD.
[c]Model 3 adjusted for age, age square, gender, ethnicity, education, Townsend index, smoking status, drinking status, physical activity, obesity, cholesterol, vitamin D, C-reactive protein, history of diabetes, history of hypertension and history of CVD.
Significant associations ($P < .05$) are bolded.

(*P*-overall = .009, *P*-nonlinear = .075, Supplementary data, Fig. S2).

Association of retinal age gap with CKD incidence

From 35 039 participants who did not have CKD at baseline, a total of 1007 participants (2.87%) developed CKD over a median (interquartile range) follow-up duration of 11.41 (11.30–11.55) years. Participants who developed CKD had higher C-reactive protein and were more likely to be male, older, smokers, non-drinkers and obese at baseline. A higher prevalence of diabetes, hypertension and CVD, but lower education, eGFR and physical activity at baseline was associated with a higher incidence of CKD during follow-up. Other baseline characteristics for the study population are provided in Supplementary data, Table S2. In the longitudinal analysis (Table 3), each 1-year increase in

Table 3: Association between retinal age gap and CKD incidence.

		Model 1[a]		Model 2[b]		Model 3[c]	
Retinal age gap	Total	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Retinal age gap, per one age (year)	35 039	1.02 (1.01–1.04)	**.008**	1.02 (1.01–1.04)	**.008**	1.03 (1.01–1.05)	**.004**
Quartiles of retinal age gap							
Q1	8760	Reference		Reference		Reference	
Q2	8760	1.13 (0.97–1.32)	.126	1.10 (0.92–1.30)	.297	1.12 (0.94–1.34)	.192
Q3	8760	1.34 (1.12–1.61)	**.002**	1.30 (1.07–1.59)	**.010**	1.35 (1.10–1.66)	**.004**
Q4	8759	1.48 (1.17–1.88)	**.001**	1.50 (1.16–1.95)	**.002**	1.54 (1.18–2.00)	**.001**
Excluding incident CKD within 2 years							
Retinal age gap, per one age (year)	34 828	1.02 (1.01–1.04)	**0.005**	1.03 (1.01–1.05)	**0.004**	1.03 (1.01–1.05)	**0.003**
Quartiles of retinal age gap							
Q1	8707	Reference		Reference		Reference	
Q2	8707	1.14 (0.97–1.34)	0.103	1.10 (0.92–1.31)	0.295	1.12 (0.94–1.34)	0.203
Q3	8707	1.33 (1.10–1.60)	**0.003**	1.30 (1.06–1.60)	**0.011**	1.35 (1.10–1.67)	**0.005**
Q4	8707	1.52 (1.19–1.94)	**0.001**	1.55 (1.19–2.02)	**0.001**	1.58 (1.21–2.07)	**0.001**

The first quartile (Q1) is defined as the set of data between the smallest value and the 25th retinal age gap. The second quartile (Q2) is the set of data between the 25th and median value. The third quartile (Q3) is set of data between the median value and the 75th retinal age gap. The fourth quartile (Q4) is defined as the set of data between the 75th and the maximum of the retinal age gap.

[a]Model 1 adjusted for age, gender and ethnicity.

[b]Model 2 adjusted for age, gender, ethnicity, education, Townsend index, smoking status, drinking status, physical activity, obesity, eGFR, cholesterol, vitamin D, C-reactive protein, history of diabetes, history of hypertension and history of CVD.

[c]Model 3 adjusted for age, age square, gender, ethnicity, education, Townsend index, smoking status, drinking status, physical activity, obesity, eGFR, cholesterol, vitamin D, C-reactive protein, history of diabetes, history of hypertension and history of CVD.

Significant associations ($P < .05$) are bolded.

retinal age gap was associated with an increased 3% risk of incident CKD [hazard ratio (HR) 1.03, 95% CI 1.01–1.05, $P = .004$] after confounders were adjusted. Meanwhile, the risk of incident CKD in participants with retinal age gap in the third (HR 1.35, 95% CI 1.10–1.66, $P = .004$) and fourth quartiles (HR 1.54, 95% CI 1.18–2.00, $P = .001$) were significantly higher than that of the lowest quartile. Similar findings were found after CKD that developed within 2 years of follow-up was excluded (Table 3). Overall, the association between retinal age gap was observed in the restricted cubic splines analysis (*P*-overall <.001, *P*-nonlinear = .025, Supplementary data, Fig. S3). This association between retinal age gap and incident CKD was significant only when retinal age gap exceeded –4.5 years (HR 1.06, 95% CI 1.03–1.10, $P < .001$).

Associations of retinal age gap with CVD complications in CKD patients

Among the 702 patients with CKD at baseline, 111 patients (15.81%) developed CVD complications during a median (interquartile range) follow-up of 11.35 (11.23–11.51) years. Supplementary data, Table S3 describes the baseline characteristics of participants with and without incident CVD events. A significant association between retinal age gap and incident CVD was observed in CKD patients after age, gender and ethnicity were adjusted (HR 1.11, 95% CI 1.04–1.17, $P = .001$, Table 4). This association remained after confounders were adjustment. Each 1-year increase in retinal age gap was associated with a 10% increase in the risk of incident CVD complication (HR 1.10, 95% CI 1.03–1.17, $P = .005$). Compared with CKD patients with retinal age gap in the lowest quartile, those with retinal age gap in the second, third and fourth quartiles had a 105%, 131% and 156% increased risk of incident CVD. As shown in Table 4, the association between retinal age gap and incident CVD remained significant CVD cases that developed within 2 years of follow-up were excluded. The restricted cubic splines analysis indicated overall relationship between retinal age gap and incident CVD (*P*-overall = .026, *P*-nonlinear = .583, Supplementary data, Fig. S4).

Predictive value of retinal age and established prediction equations for CVD risk in CKD patients

The predictive value of retinal age-based models and risk factor-based models in future CVD risk in CKD patients were described in Supplementary data, Fig. S5. The AUC of retinal age-based model was 0.664 (95% CI 0.588–0.740), which was comparable to the AUC of the American College of Cardiology/American Heart Association PCEs model (AUC 0.666, 95% CI 0.588–0.745) and the CRIC clinical model (AUC 0.679, 95% CI 0.600–0.761). There was no significant difference between each model ($P = .170$).

DISCUSSION

In a large population of middle-aged and older adults, we found that each 1-year increase in retinal age gap was independently associated with a 2% and 3% increase in the risk of prevalence and incidence of CKD, respectively, and was also independently associated with a 10% higher risk of future CVD complications in CKD patients. This has demonstrated that the retinal age gap may be a non-invasive, convenient and universal marker for predicting CKD and its CVD complications.

Our study supported the retina as a good window to non-invasively observe CKD and its CVD complications. Previous studies have described retinal microvascular changes, including increased retinal venular tortuosity [28], narrowed retinal arterioles [29], increased retinal arteriolar wall-to-lumen ratio [30], decreased retinal vessel density [31, 32], smaller retinal vascular fractal dimensions [33] and thinner retinal thickness [32], are closely associated with CKD or impaired kidney function. Furthermore, several DL models using fundus images have demonstrated good performance in diagnosing and predicting CKD, validating the utility and robustness of using the retina to predict

Table 4: Association between retinal age gap and subsequent CVD events in patients with CKD.

		Model 1[a]		Model 2[b]		Model 3[c]	
Retinal age gap	Total	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Retinal age gap, per one age (year)	702	1.11 (1.04–1.17)	**.001**	1.09 (1.02–1.16)	**.008**	1.10 (1.03–1.17)	**.005**
Quartiles of retinal age gap							
Q1	176	Reference		Reference		Reference	
Q2	175	2.37 (1.37–4.09)	**.002**	1.99 (1.12–3.53)	**.020**	2.05 (1.15–3.65)	**.015**
Q3	176	2.31 (1.27–4.22)	**.006**	2.06 (1.09–3.86)	**.021**	2.31 (1.21–4.42)	**.012**
Q4	175	2.89 (1.47–5.67)	**.002**	2.24 (1.10–4.58)	**.033**	2.56 (1.22–5.37)	**.013**
Excluding incident CVD within 2 years							
Retinal age gap, per one age (year)	683	1.10 (1.03–1.17)	**.004**	1.09 (1.02–1.17)	**.012**	1.09 (1.02–1.17)	**.012**
Quartiles of retinal age gap							
Q1	171	Reference		Reference		Reference	
Q2	171	2.39 (1.35–4.27)	**.003**	2.21 (1.21–4.04)	**.010**	2.22 (1.22–4.07)	**.009**
Q3	171	2.46 (1.30–4.66)	**.006**	2.36 (1.21–4.58)	**.012**	2.42 (1.22–4.79)	**.011**
Q4	171	3.10 (1.50–6.39)	**.002**	2.54 (1.18–5.46)	**0.017**	2.61 (1.19–5.71)	**.016**

The first quartile (Q1) is defined as the set of data between the smallest value and the 25th retinal age gap. The second quartile (Q2) is the set of data between the 25th and median value. The third quartile (Q3) is set of data between the median value and the 75th retinal age gap. The fourth quartile (Q4) is defined as the set of data between the 75th and the maximum of the retinal age gap.

[a]Model 1 adjusted for age, gender and ethnicity.

[b]Model 2 adjusted for age, gender, ethnicity, education, Townsend index, smoking status, drinking status, physical activity, obesity, eGFR, cholesterol, vitamin D, C-reactive protein, history of diabetes and history of hypertension.

[c]Model 3 adjusted for age, age square, gender, ethnicity, education, Townsend index, smoking status, drinking status, physical activity, obesity, eGFR, cholesterol, vitamin D, C-reactive protein, history of diabetes and history of hypertension.

Significant associations ($P < .05$) are bolded.

CKD [34, 35]. Similarly, in CKD patients, enlarged retinal venous diameter [36], the presence and severity of retinopathy [36], and the retinopathy progression [37] can increase the risk of future CVD complications. These findings support our results, indicating that retinal features may be used for early detection of high-risk CKD patients and its CVD complications.

Our study demonstrated that retinal age gap, an aging biomarker derived from retinal images, was closely linked to changes associated with kidney damage. Although our previous findings reported an association between retinal age gap and end-stage renal disease [38], this study highlights the role of retinal age gap in predicting CKD and its CVD complications, favoring early personalized intervention in high-risk patients which is more important for reducing the morbidity and mortality of CKD. Additionally, retinal age gap has the advantages of non-invasive, convenient and universal—advantages which are lacking in cellular, molecular and other image-based aging biomarkers.

Currently, several mainstream mechanisms explain the close association among the retina, kidneys and cardiovascular system. First, the microvasculature of the retina and kidneys have a high homogeneity, and both are important components of the cardiovascular system [16]. Peripheral microvascular dysfunction damages the visceral microvascular bed, and changes the microvascular structure and function that can occur before end-organ damage and complications of CVD [39–41]. Secondly, endothelial dysfunction is a common component in inducing retinal lesions, CKD and CVD [16]. During the development of CKD, there is an accumulation of oxidative stress, inflammation, uremic toxins and other factors that contribute to endothelial cell structural damage, making patients more susceptible to CVD complications [41–44]. These pathological mechanisms are also associated with retinal changes in CKD patients [45]. Further, excessive oxidative stress, lipid accumulation and chronic inflammation caused by aging can also lead to endothelial dysfunction [46], resulting in related retinal and kidney changes [47, 48]. Meanwhile, CKD is also a manifestation of premature aging in the body, which can accelerate aging of the retina and cardiovascular system [47–49]. Moreover, the retinal age gap has been demonstrated as a biomarker of arteriosclerosis [22]. It may also reflect the vascular aging of the kidney, as well as the cardiovascular and cerebrovascular aging following CKD.

Our study's baseline characteristics revealed intriguing associations between retinal age gap and certain health conditions that may seem counterintuitive. Intuitively, among participants without CKD, individuals with a great retinal age gap had higher eGFR levels at baseline and were less likely to have hypertension and CVD. However, it has been found that these intuitive relationships do not accurately reflect the true associations. This is because the incidence of CKD and CVD can be influenced by various factors, such as age, gender, genetics, lifestyle and comorbidities. Furthermore, the temporal relationship between retinal age gap and hypertension/CVD may also impact these associations. Further research is required to comprehend the intricate connections between retinal aging, kidney function and various cardiovascular outcomes, as well as to determine their underlying mechanisms. Additionally, we discovered that the association between retinal age gap and CKD-related outcomes was not modified by diabetes, hypertension and baseline eGFR (Supplementary data, Table S4), indicating the independent effect of retinal age gap on CKD and CVD complications.

The early identification of CKD and its CVD complications is important for early intervention and management. Our study suggests retinal age gap is a valuable biological marker of aging with great potential in identifying high-risk CKD individuals, and more importantly, it has implications for predicting CVD complications. The non-invasive and convenient nature of retinal imaging means the retinal age gap is a practical, convenient and accessible tool that can be easily applied in clinical and community screening. Additionally, the intelligent screening project for eye diseases based on fundus images has been implemented

in the real world and has achieved preliminary success [50, 51]. The potential use of the retinal age gap has potential to further enhance the health and economic benefits of these in the community and promote eye and kidney health.

The strengths of this study included a large sample size, long follow-up time, comprehensively adjusted for confounding factors, and a standard collection of retinal images. However, there were also some limitations. First, the UK Biobank cohort consisted of younger and healthier participants, and the study only included those who had available retinal images from this cohort. This may have resulted in selection bias and could impact the generalizability of the findings. Nonetheless, this did not change the association between retinal age gap and the primary outcomes. Secondly, there was no other cohort data for external validation. Therefore, future studies in different populations are needed to validate our findings. Moreover, due to the limited longitudinal data available on retinal images, we could not explore the dynamic changes in retinal age gap and its association with CKD or CVD complications. Third, the use of one-time eGFR values to estimate the CKD prevalence may introduce some bias, as it may include cases of acute kidney injury. Fourthly, future research is needed to validate the generalizability of our findings to all stages of CKD. Finally, while we adjusted for a large number of potential confounding factors in our analysis, we were unable to exclude the possible effects of unmeasured confounding on our findings.

In conclusion, this study demonstrates that retinal age gap is independently associated with the incidence and prevalence of CKD, as well as the incidence of CVD in CKD patients. As an aging biomarker, retinal age gap has great potential in identifying individuals at high risk for CKD and its CVD complications, thus allowing for personalized prevention and management of CKD along with its CVD complications.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

Conception and design: Z.T.Z., Y.J.H., H.H.Y., X.H.Y. Analysis and interpretation: G.R.W., X.Y.Z., Y.J.H. Data collection and collation: G.R.W., Z.T.Z., Y.Y.L., Y.X.W., Z.J.D. Statistical analysis: G.R.W. Drafting of the manuscript: G.R.W. Critical revision of the manuscript for important intellectual content: Z.T.Z., X.Y.Z., G.A.B., C.W.Z., Y.J.H. Study supervision: Y.J.H., H.H.Y., Y.H., X.W.S. All authors revised and approved the submitted manuscript.

DATA AVAILABILITY STATEMENT

This project corresponds to UK Biobank application ID#86091. Data from the UK Biobank dataset are available at https://www.ukbiobank.ac.uk/ by application.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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