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ORIGINAL ARTICLE

# Association between deep-learning-derived retinal aging speed and rapid decline of renal function in the Japanese general population

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## ABSTRACT

**Background.** The eye and the kidney share microvascular features, and retinal changes have been postulated to reflect systemic cardiometabolic dysfunction. Recently, retinal age, estimated by deep learning (DL) from a single fundus photograph, has been shown to predict cardiovascular events. The present study aimed to determine whether retinal aging speed, defined as the individual-specific annual rate of change in DL-estimated retinal age, is associated with rapid estimated glomerular filtration rate (eGFR) decline.

**Methods.** We retrospectively analyzed the longitudinal data obtained from 7807 Japanese individuals who underwent repeated health check-ups with serial measurements of eGFR and fundus photographs (median 9.0 visits over median 8.0 years). We evaluated the relationship between retinal aging speed during the baseline period (from baseline to year 4) and rapid eGFR decline ($\leq -3$ ml/min/1.73 m$^2$/year) during the follow-up period (after year 4).

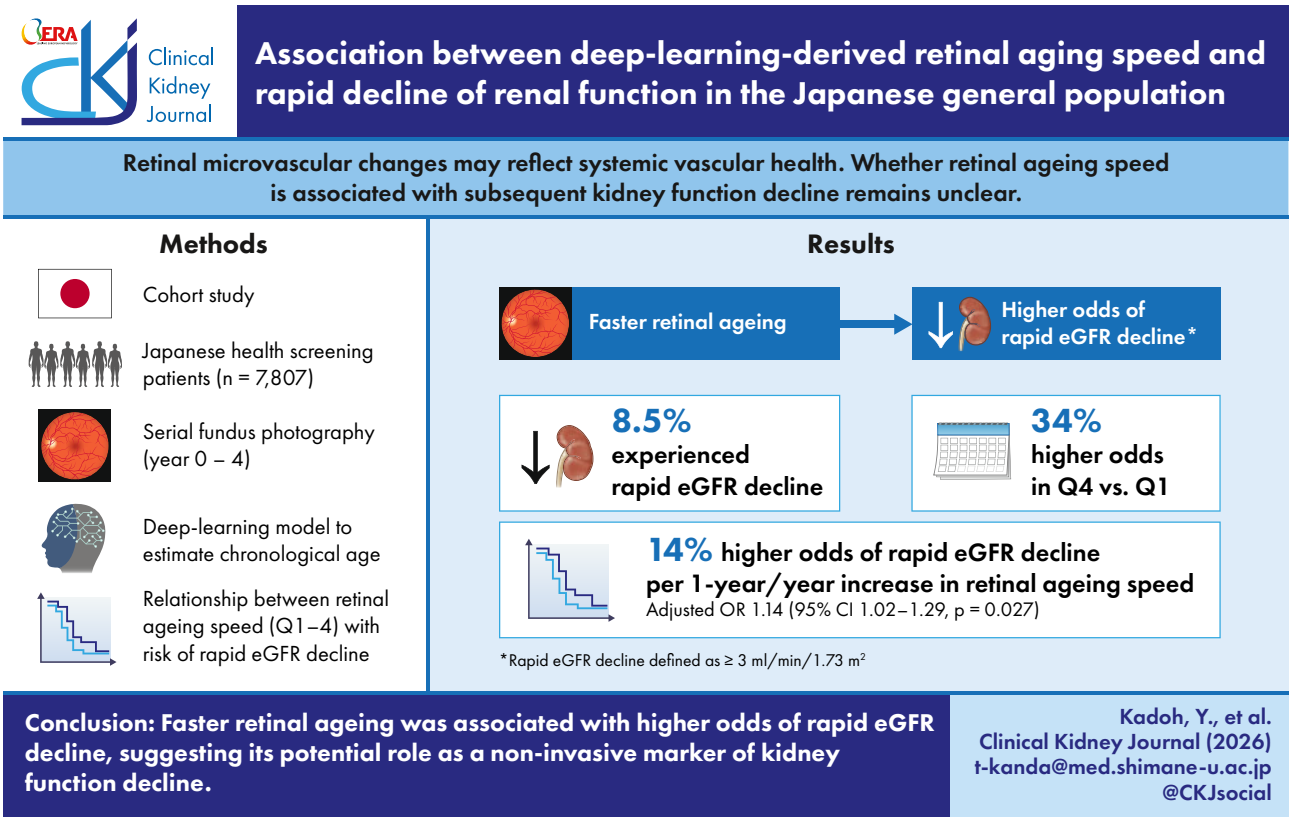
**Results.** The incidence of rapid eGFR decline was significantly higher in the highest quartile of retinal aging speed than in the lowest quartile as the reference group in the fully adjusted model adjusting age, sex, body mass index, blood pressure, diabetes, smoking, eGFR, and proteinuria [odds ratio (OR) 1.34; 95% confidence interval (CI) 1.06–1.68; $P = .015$]. In the multivariable logistic regression models, retinal aging speed was associated with rapid eGFR decline after adjusting multiple key confounders (OR 1.14; 95% CI 1.02–1.29; $P = .027$).

**Conclusions.** Taken together, DL-derived retinal aging speed is independently associated with rapid eGFR decline in the Japanese general population.

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## GRAPHICAL ABSTRACT




**Keywords:** artificial intelligence, chronic kidney disease, deep learning, rapid eGFR decline, retinal aging speed

## KEY LEARNING POINTS

**What was known:**

- The eye and the kidney share microvascular features and retinal changes have been postulated to reflect systemic cardiometabolic dysfunction.
- Rapid estimated glomerular filtration rate (eGFR) decline is a risk factor of end-stage renal disease, cardiovascular events, and death.

**This study adds:**

- Retinal aging speed, defined as the individual-specific annual rate of change in deep-learning-estimated retinal age, is associated with the incidence of rapid eGFR decline in the Japanese general population.

**Potential impact:**

- Artificial-intelligence-based assessment of retinal aging speed from serial fundus photographs may provide a non-invasive approach to identifying individuals at increased risk of rapid eGFR decline and could complement conventional kidney risk stratification.

## INTRODUCTION

Chronic kidney disease (CKD), a growing global health problem [1], is increasingly driven by population aging [2]. Age-related decline in glomerular filtration rate (GFR) contributes to the development of end-stage renal disease (ESRD), cardiovascular disease, and death [1, 3, 4]. Nevertheless, the trajectory of kidney function decline varies among individuals [5, 6]. Whereas many people experience stable or slowly progressive decline in renal function, a subset shows rapid decline, which is an independent risk factor of ESRD, cardiovascular events, and death [3, 4, 6]. Accumulating evidence has suggested that conventional risk factors such as age, hypertension, diabetes, obesity, proteinuria, and dyslipidemia are important predictors of rapid renal function decline; however, they may not fully capture inter-individual differences [7]. Therefore, discovery of a new surrogate marker for identifying individuals at risk for rapid GFR decline before overt CKD develops is a key clinical and public health challenge [8].

The retina provides a unique, non-invasive window into the systemic microcirculation [9, 10], and retinal microvascular changes have therefore been proposed as surrogate markers of systemic microvascular function [9, 10]. Indeed, recent prospective longitudinal studies demonstrate the relationship between retinal vessel measurements and age-related GFR decline in non-diabetic individuals [11].

With advances in deep learning (DL), fundus photographs have become a scalable substrate for retina-derived biomarkers, including DL-based estimation of retinal age [12]. Previous studies have revealed the relationship between the retinal age gap, defined as the difference between DL-predicted retinal age and chronological age, the risk of all-cause mortality and cardiovascular events, and adverse renal outcomes including incident CKD and ESRD [13–15]. In addition, recent studies have shown that DL models that involve fundus images may support the detection of diabetic kidney disease and adverse renal outcomes [16] and retina-derived artificial intelligence (AI) approaches have provided promise for detecting prevalent CKD and supporting CKD risk stratification [17]. However, the relationship between retina-derived aging metrics and longitudinal kidney function trajectories remains unexplored.

The major purpose of the present study was to determine whether retinal aging speed, defined as the individual-specific annual rate of change in DL-estimated retinal age [12], is associated with the risk of rapid decline in renal function. To this end, we retrospectively analyzed data obtained from a large health-screening cohort that involved the serial measurements of estimated GFR (eGFR) and fundus photographs and evaluated the relationship between the DL-derived retinal aging speed and rapid eGFR decline in the general population.

## MATERIALS AND METHODS

### Study population

This was a retrospective observational cohort study conducted at the General Hospital and Seirei Center for Health Promotion and Preventive Medicine in Japan. This study has been approved by the institutional review boards of Seirei Hamamatsu General Hospital and Seirei Center for Health Promotion and Preventive Medicine (#04-08) and Shimane University (#20250521-3) and it was conducted according to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants included in the study. The cohort database included 467 408 fundus examinations from 64 636 subjects who participated in a health examination system in the Seirei Center for Health Promotion and Preventive Medicine from 7 May 2012 to 31 March 2021. Most participants were the residents of Hamamatsu City where the hospital was located, and the neighboring regions. Although racial or ethnic identification was not documented in the study, almost all of the participants were Japanese. We considered subjects eligible for the retinal age assessments if they received at least eight repeated examinations during the study period. All retinal images were carefully evaluated by the board-certified ophthalmologists [18]. We excluded images showing optic nerve head abnormalities, such as optic nerve or optic nerve head hypoplasia and optic nerve pit, and retinal pathologies, such as retinal detachment, age-related macular degeneration, myopic macular degeneration, macular hole, diabetic retinopathy, and arterial or venous occlusion, since such structural changes could distort DL-based estimation of retinal age. High myopia, in the absence of these associated fundus abnormalities, was not excluded. After the evaluation of fundus photographs, 91 190 eligible fundus photographs from 10 445 participants were subjected to retinal age analyses. For each participant, the first 4 years after their initial examination were defined as the baseline period, during which retinal aging speed was estimated using serial fundus photographs. The study period after year 4 was defined as the follow-up period, during which the eGFR slope and renal outcome were evaluated. The observation period was divided at year 4, approximately the midpoint of the median 8-year observation period, so that comparable intervals were available for estimating retinal aging speed and the subsequent eGFR slope. Among the eligible population, 161 were excluded because they did not meet the criteria for estimating retinal aging speed, 2181 were excluded because they did not meet the criteria for estimating eGFR slope, and 296 were excluded because their total follow-up duration was $<7$ years. No participant was excluded due to missing covariate data; complete data were available for all variables included in the models, and no imputation was performed. Consequently, 7807 participants were included in the final analysis (Fig. S1).

### Model training and retinal age estimation

We trained a DL model to estimate chronological age from color fundus photographs. The target variable was the participant's age at the time of image acquisition. To avoid data leakage, we used a five-fold cross-validation scheme at the patient level (training:test = 4:1), such that all images from the same patient were assigned to the same fold. To obtain a more balanced distribution of age across folds, baseline age values were divided into deciles using quantile-based binning and used as stratification labels during cross-validation.

All fundus photographs were acquired with the same non-mydriatic fundus camera with a 45° field of view (DG-10, Canon, Tokyo, Japan) according to a standardized imaging protocol at the health check-up center. Neither the camera nor the imaging protocol was changed during the study period. Fundus photographs (651 × 651 pixels) were processed using PyTorch. During training, images were randomly resized and cropped to 456 × 456 pixels (scale 0.90–1.00), with random horizontal and vertical flipping and ±20° rotation. During evaluation, images were resized to 480 × 480 pixels and center-cropped to 456 × 456 pixels without augmentation. We used an EfficientNet-B5 backbone (tf_efficientnet_b5.ns_jft_in1k, timm implementation) [19], pre-trained on ImageNet-1k and unlabeled JFT-300M using Noisy Student semi-supervised learning [20]. The classification head was replaced with a single fully connected layer outputting a continuous age value. The network was trained using mean squared error loss and the Adam optimizer. The learning rate was fixed at 0.0001, and the model was trained for two epochs (batch size = 8). Pixel intensities were normalized using the mean and standard deviation of the ImageNet pre-training dataset.

Each fundus photograph was paired with the corresponding chronological age at the time of imaging. When multiple images were available from the same patient (including both eyes and repeated visits), all images were included as separate training samples. Predicted ages were obtained for the entire dataset using patient-level five-fold cross-validation. For each fold, the model was trained on the remaining four-folds and applied only to the held-out fold, ensuring that every image was evaluated by a model that had not seen data from the same patient. DL-derived retinal age was estimated separately for each photograph, and we calculated the average values from both eyes at each visit. DL model estimated chronological age with a mean

absolute error of 2.99 years, a root mean squared error of 3.88 years, a Pearson correlation of 0.921 ($P < .001$) across 171 725 held-out predictions.

### Measurement of retinal aging speed

Retinal aging speed was defined as the individual-specific annual change in DL-derived retinal age during the baseline period (from baseline to year 4) (Fig. S2). DL-derived retinal age values were averaged at each visit, and retinal aging speed was calculated as the slope of an ordinary least-squares regression of this visit-level mean retinal age on time since baseline. Accordingly, retinal aging speed was considered as the rate at which predicted retinal age advances relative to the passage of chronological time, in years per year: a value of 1.0 indicates that predicted retinal age advances in step with chronological age, whereas values above or below 1.0 indicate apparently accelerated or decelerated retinal aging. To ensure the accuracy of slope estimation, retinal aging speed was calculated only for participants with at least three valid visit-level retinal age measurements spanning at least 2 years during the baseline period.

### Renal outcome

We used the creatinine-based Japanese eGFR equation because it was developed and validated for Japanese adults and is routinely used in Japanese clinical and epidemiological studies [21]. eGFR slope was defined as the annual change in eGFR during the follow-up period (after year 4) and was estimated for each participant using ordinary least-squares regression based on eGFR measurements obtained after year 4. To ensure the accuracy of slope estimation, eGFR slope was calculated only for participants with at least three eGFR measurements obtained after year 4 spanning at least 2 years [22]. Rapid eGFR decline was defined as an individualized eGFR slope of $\leq -3.0$ ml/min/1.73 $m^2$/year (equivalent to an annual eGFR loss of $\geq$3.0 ml/min/1.73 $m^2$/year), based on the prior epidemiologic studies that used this threshold to define rapid kidney function decline and linked it to adverse cardiovascular events and death [3, 4].

### Statistical analyses

Baseline covariates, including age, sex, body mass index (BMI), systolic blood pressure, diabetes [defined as hemoglobin A1c (HbA1c) of 6.5% or higher or use of glucose-lowering drugs], current smoking, eGFR, and proteinuria, were obtained from health-checkup measurements at the initial examination. Analyses were performed using complete-case data for variables included in each model, and no imputation was performed. To evaluate the independent association between retinal aging speed and rapid eGFR decline, we performed stepwise multivariable logistic regression analyses and estimated odds ratios (ORs) and 95% confidence intervals (CIs). The exposure was evaluated in two ways: as a continuous variable per 1.0 years/year increase, and as quartiles (secondary: Q1–Q4). Four stepwise adjustment models were constructed: Model 1, unadjusted; Model 2, adjusted for age, sex, and BMI; Model 3, Model 2 plus systolic blood pressure, diabetes, and current smoking; Model 4, Model 3 plus eGFR and proteinuria. The association between retinal aging speed and annual eGFR slope was assessed using Pearson's and Spearman's correlation coefficients.

Statistical analyses were performed using R (version 4.5.2; The Foundation for Statistical Computing, Vienna, Austria). A two-sided $P$-value of $<.05$ was considered statistically significant.

## RESULTS

### Baseline characteristics

The baseline characteristics of 7807 participants enrolled in the study were summarized in Table 1. The median age was 52 [interquartile range (IQR), 45–59] years, 65.8% were men, and 17.0% were smokers. The median systolic blood pressure was 114 (IQR, 104–126) mmHg, median HbA1c was 5.5% (IQR, 5.2%–5.7%), median low-density lipoprotein (LDL) cholesterol concentration was 127 (IQR, 107–148) mg/dL, median eGFR was 75.5 (IQR, 67.6–84.6) mL/min/1.73 $m^2$, and the proportion of proteinuria was 1.8%. The proportions of the patients who had CKD, defined as GFR <60 ml/min/1.73 $m^2$ and/or proteinuria, and diabetes, were 10.7% and 5.0% respectively. Although we found statistically significant but marginal differences in age and BMI between participants who were excluded from the analysis and those who were included in the analysis, both groups overall had similar baseline clinical characteristics (Table S1).

Retinal aging speed was estimated using a median of eight fundus photographs (IQR, 8–10) obtained at 4 (IQR, 4–5) visits per participant over a median assessment period of 3.34 years (IQR, 3.05–3.93). The median retinal aging speed was 1.03 (IQR, 0.62–1.44) years/year ranging from −2.22 to 4.95 years/year. A scatter plot of retinal aging speed and annual eGFR slope with a fitted linear regression line is shown in Fig. S3. We found that retinal aging speed and the annual eGFR slope showed statistically significant but negligible correlations (Pearson $r = -0.025$, $P = .025$; Spearman $\rho = -0.027$, $P = .016$). In multivariable linear regression treating the annual eGFR slope as a continuous outcome, the association did not reach statistical significance ($\beta = -0.068$, 95% CI −0.146 to 0.010, $P = .087$).

We next stratified the participants according to the quartiles of retinal aging speed. The 7807 participants were distributed nearly equally across the four quartiles: 1952 in Q1, 1952 in Q2, 1952 in Q3, and 1951 in Q4. Across quartiles, the proportion of smoking habit and eGFR were significantly higher with faster retinal aging speed ($P$-trend $< .001$) and age showed significant but non-monotonic trend ($P$-trend= .001) (Table 1). Other parameters, such as sex, BMI, systolic blood pressure, LDL cholesterol, and proteinuria, did not vary among the quartiles.

During a median follow-up of 3.15 years (IQR, 3.00–3.98) after year 4, 665 individuals (8.5%) experienced rapid eGFR decline ($\leq$ −3 ml/min/1.73 $m^2$/year) and the incidence of rapid eGFR decline was significantly higher in the individuals who had a higher retinal aging speed ($P$-trend= .013) (Table 1). The risk of rapid eGFR decline was significantly higher in the highest quartile (Q4) than in the lowest quartile (Q1) as the reference group in the fully adjusted model including age, sex, BMI, systolic blood pressure, diabetes, smoking habit, eGFR, and proteinuria (Model 4: OR 1.34; 95% CI 1.06–1.68; $P = .015$) (Table 2). We found that retinal aging speed was significantly associated with rapid eGFR decline after excluding participants with CKD (Model 4: OR 1.15, 95% CI 1.01–1.30; $P = .033$). In addition, we performed a sensitivity analysis using an alternative definition of rapid kidney function decline, an annual eGFR slope $\leq -5.0$ ml/min/1.73 $m^2$/year. We found the similar association between retinal aging speed and the incidence of rapid eGFR decline (129 events; Model 4: OR 1.32; 95% CI 1.03–1.70; $P = .029$).

Table 3 presents the sequentially adjusted multivariable logistic regression models for rapid eGFR decline as a continuous variable per 1.0 years/year increase. In the unadjusted model, retinal aging speed was positively associated with a higher incidence of rapid eGFR decline (OR 1.18; 95% CI 1.05–1.33; $P = .006$), and this association remained significant even after

**Table 1: Baseline characteristics.**

| Variable | | Total $n = 7807$ | Q1 $n = 1952$ | Q2 $n = 1952$ | Q3 $n = 1952$ | Q4 $n = 1951$ | P-trend |
|---|---|---|---|---|---|---|---|
| Retinal aging speed, years/year | Median [IQR] | 1.03 [0.62–1.44] | 0.31 [0.04–0.48] | 0.83 [0.73–0.94] | 1.22 [1.12–1.33] | 1.75 [1.57–2.03] | |
| Age, years | Median [IQR] | 52 [45–59] | 54 [48–62] | 51 [44–58] | 50 [44–59] | 52 [45–59] | <.001 |
| Male sex | *n* (%) | 5138 (65.8) | 1266 (64.9) | 1270 (65.1) | 1298 (66.5) | 1304 (66.8) | .124 |
| BMI, kg/m$^2$ | Median [IQR] | 22.4 [20.4–24.5] | 22.3 [20.4–24.4] | 22.4 [20.3–24.6] | 22.4 [20.6–24.4] | 22.4 [20.4–24.6] | .215 |
| Current smoking | *n* (%) | 1330 (17.0) | 284 (14.5) | 310 (15.9) | 336 (17.2) | 400 (20.5) | <.001 |
| Systolic blood pressure, mmHg | Median [IQR] | 114 [104–126] | 114 [104–126] | 114 [104–124] | 112 [102–124] | 114 [104–126] | .165 |
| HbA1c, % | Median [IQR] | 5.5 [5.2–5.7] | 5.5 [5.2–5.7] | 5.5 [5.2–5.7] | 5.5 [5.2–5.7] | 5.5 [5.2–5.7] | .076 |
| LDL cholesterol, mg/dl | Median [IQR] | 127 [107–148] | 129 [109–149] | 126 [106–146] | 126.0 [107–145] | 127 [108–150] | .308 |
| Proteinuria | *n* (%) | 139 (1.8) | 37 (1.9) | 33 (1.7) | 31 (1.6) | 38 (1.9) | .850 |
| eGFR, ml/min/1.73 m$^2$ | Median [IQR] | 75.5 [67.6–84.6] | 75.3 [67.1–84.0] | 75.1 [67.6–84.1] | 75.6 [68.1–84.7] | 76.2 [67.8–85.1] | <.001 |
| eGFR slope, ml/min/1.73 m$^2$/year | Median [IQR] | −0.45 [−1.57 to 0.71] | −0.43 [−1.52 to 0.70] | −0.45 [−1.63 to 0.74] | −0.43 [−1.49 to 0.77] | −0.55 [−1.69 to 0.64] | .040 |
| Rapid decliner | *n* (%) | 665 (8.5) | 139 (7.1) | 176 (9.0) | 160 (8.2) | 190 (9.7) | .013 |

Note: Values are presented as median [IQR] or *n* (%), as appropriate. Quartile boundaries for retinal aging speed were Q1, ≤0.622 years/year; Q2, >0.622 to ≤1.027 years/year; Q3, >1.027 to ≤1.436 years/year; and Q4, >1.436 years/year. Retinal aging speed was defined as the annual change in deep-learning-predicted retinal age from baseline to year 4; the person-level value was calculated as the slope of visit-level mean retinal age. Participants were categorized into quartiles of retinal aging speed, with Q1 representing the slowest and Q4 the fastest group. *P* for trend was calculated by modeling quartile number as an ordinal variable, using linear regression for continuous variables and logistic regression for binary variables. Baseline proteinuria was defined as dipstick proteinuria ≥1+ or semiquantitative urine protein ≥30 mg/dl. eGFR was calculated using the Japanese equation. Rapid eGFR decline was defined as an eGFR slope ≤ −3.0 ml/min/1.73 m$^2$/year after year 4.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; IQR, interquartile range; LDL, low-density lipoprotein.

fully adjusting multiple key confounders including diabetes status (Model 4: OR 1.14; 95% CI 1.02–1.29; $P = .027$).

## DISCUSSION

Our results are consistent with data obtained from a series of studies that evaluated the relationship between retinal vascular structure and renal outcomes [23]. For example, Småbrekke *et al*. recently reported that central retinal arteriolar and venular equivalents are associated with age-associated GFR decline in a nondiabetic population. Such measurements have the advantage of anatomical interpretability. In addition, population-based analyses have reported associations between a static retinal age gap and incidences of CKD and kidney failure [13]. In the present study, we further extended the paradigm by shifting from static measurements to a dynamic framework, operationalizing an individual-specific rate of change derived from repeated AI-estimated retinal age measurements. Whereas standard measurements evaluate specific focal parameters like vessel calibers, DL models holistically integrate complex, non-linear structural alterations and subtle subclinical features across the entire retina. Therefore, retinal aging speed, calculated from serial DL-estimated retinal age measurements, is expected to enable us to capture dynamic progression rather than the established retinal vascular biomarkers. Supporting the notion, recent longitudinal evidence suggests that within-person changes in retinal aging metrics provide greater prognostic information than baseline values alone [24, 25].

The mechanisms responsible for the relationship between retinal aging speed and rapid eGFR decline remain unclear but could be explained by the common microvascular pathophysiological features between eye and kidney [9, 10]. Both the retinal microvasculature and the renal glomeruli are low-resistance, high-flow systems that are highly susceptible to systemic hemodynamic fluctuations and metabolic disturbances such as oxidative stress and inflammation, leading to the development of endothelial dysfunction and microvascular rarefaction [26]. We therefore speculate that accelerated longitudinal retinal aging speed may serve as an early and visible marker for the identification of individuals predisposed to systemic and renal microvascular injury before overt clinical deterioration occurs.

There are several limitations in this study. First, the causal relationship between retinal aging speed and subsequent rapid eGFR decline remains unknown due to the nature of this observational study and it might be confounded by clinical factors not assessed in the present study, such as urine microalbumin concentration, hematuria, and use of renoprotective drugs such as renin–angiotensin system inhibitors, sodium–glucose co-transporter 2 inhibitors, and mineralocorticoid receptor antagonists. Second, the quartile-based association was not strictly monotonic, suggesting that the relationship may not be linear across the full range of retinal aging speed. However, it should be noted that the association remained significant when retinal aging speed was analyzed as a continuous variable after adjustment for key clinical covariates. Third, almost all of our cohort participants in this study were Japanese people who serially received the health check-up at a single center, which may introduce selection bias and limit the generalizability. Fourth, detailed information on the underlying causes of CKD was not available in this health-screening database. Although the association remained significant after excluding participants with CKD, we cannot exclude the possibility that unmeasured kidney pathologies affected both retinal features and kidney outcomes. Fifth, DL models could be susceptible to overfitting,

**Table 2: Association of retinal aging speed quartiles with rapid eGFR decline.**

| Model | | Q1 | Q2 | Q3 | Q4 | P-trend |
|---|---|---|---|---|---|---|
| Model 1 | OR (95% CI) | Reference | 1.29 (1.03–1.63) | 1.16 (0.92–1.48) | 1.41 (1.12–1.77) | .013 |
| | P-value | | P = .030 | P = .207 | P = .003 | |
| Model 2 | OR (95% CI) | Reference | 1.26 (1.00–1.59) | 1.13 (0.89–1.44) | 1.38 (1.10–1.74) | .020 |
| | P-value | | P = .055 | P = .307 | P = .006 | |
| Model 3 | OR (95% CI) | Reference | 1.25 (0.99–1.58) | 1.12 (0.89–1.43) | 1.34 (1.07–1.69) | .039 |
| | P-value | | P = .060 | P = .335 | P = .012 | |
| Model 4 | OR (95% CI) | Reference | 1.29 (1.02–1.63) | 1.14 (0.90–1.45) | 1.34 (1.06–1.68) | .049 |
| | P-value | | P = .036 | P = .274 | P = .015 | |

Note: Values are odds ratios (ORs) with 95% confidence intervals (CIs). ORs were estimated using logistic regression models, with Q1 used as the reference group. Rapid eGFR decline was defined as an eGFR slope $\leq -3.0$ ml/min/1.73 $m^2$/year after year 4. P values for Q2, Q3, and Q4 were obtained from Wald tests comparing each quartile with Q1. P for trend was calculated by modeling quartile number as an ordinal variable. Model 1 was unadjusted; Model 2 was adjusted for age, sex, and BMI; Model 3 was additionally adjusted for SBP, diabetes, and current smoking; and Model 4 was further adjusted for proteinuria and eGFR.
Abbreviations: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; SBP, systolic blood pressure.

**Table 3: Association between retinal aging speed and rapid eGFR decline.**

| Model | Adjustment | OR (95% CI) | P value |
|---|---|---|---|
| Model 1 | Unadjusted | 1.18 (1.05–1.33) | .006 |
| Model 2 | Age + sex + BMI | 1.17 (1.04–1.32) | .010 |
| Model 3 | Model 2 + SBP + diabetes + smoking | 1.15 (1.02–1.30) | .020 |
| Model 4 | Model 3 + proteinuria + eGFR | 1.14 (1.02–1.29) | .027 |

Note: Values are odds ratios (ORs) with 95% confidence intervals (CIs) per 1.0 year/year increase in retinal aging speed. ORs were estimated using logistic regression models. Rapid eGFR decline was defined as an eGFR slope $\leq -3.0$ ml/min/1.73 $m^2$/year after year 4. Model 1 was unadjusted; Model 2 was adjusted for age, sex, and body mass index; Model 3 was additionally adjusted for systolic blood pressure, diabetes, and current smoking; and Model 4 was further adjusted for proteinuria and eGFR. P values were obtained from Wald tests.
Abbreviations: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; OR, odds ratio; SBP, systolic blood pressure.

dataset-specific biases, and variability in image quality across visits. In addition, although image acquisition followed a simple and standardized protocol, we cannot exclude the possibility that media opacity or quality of retinal photographs could have varied during the study period. Finally, the specific retinal features driving the DL-based retinal age estimates remain unclear. Further studies using established explainability approaches are needed to clarify the retinal structures underlying DL-derived retinal age.

In conclusion, DL-derived retinal aging speed is independently associated with rapid eGFR decline in the Japanese general population. Additional studies using externally validated AI models are warranted to determine whether retinal aging speed can contribute to kidney risk assessment beyond conventional clinical parameters.

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During the preparation of this manuscript, the authors used a generative artificial intelligence tool to assist with language editing and improvement of clarity. After using this tool, the authors reviewed, edited, and verified all content as necessary and take full responsibility for the accuracy, integrity, and originality of the work.

## AUTHORS' CONTRIBUTIONS

Conceptualization: Y.K., M.K., M.T., and T.K. Methodology: M.K. Formal analysis: Y.K. and M.K. Investigation: Y.K., J.Y., T.O., F.K., A.U., M.H., R.A., S.M., T.K., K.S., and M.T. Writing—original draft: Y.K. Writing—review & editing: all authors. Supervision: M.T. and T.K.

## SUPPLEMENTARY DATA

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

## CONFLICT OF INTEREST STATEMENT

None declared.

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## DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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