• Investigation •

Retinal nerve fiber layer defects and chronic kidney disease: the Kailuan Eye Study

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Abstract

● **AIM:** To investigate whether retinal nerve fiber layer defects (RNFLDs) is a potential risk factor for chronic kidney disease (CKD) in Chinese adults.

● **METHODS:** The Kailuan Eye Study was a population-based study that included 14 440 participants. All participants underwent detailed assessments, RNFLDs were diagnosed using color fundus photographs.

● **RESULTS:** Overall, 12 507 participants [8533 males (68.23%)] had complete systemic examination data and at least one evaluable fundus photograph. RNFLDs were found in 621 participants [5.0%; 95% confidence interval (CI): 4.6%-5.34%], and 70 cases of multiple RNFLDs were found (11.27%). After adjusting multiple factors, RNFLDs was significantly associated with CKD severity, the ORs of CKD stage 3, stage 4 and stage 5 were 1.698, 4.167, and 9.512, respectively. Multiple RNFLDs were also associated with CKD severity after adjusting multiple factors, the ORs of CKD stage 3 and stage 5 were 4.465 and 11.833 respectively. Furthermore, 2294 participants had CKD (18.34%, 95%CI: 17.68%-18.99%). After adjusting for other factors, CKD presence was significantly correlated with the presence of RNFLDs.

● **CONCLUSION:** The strongest risk factors for RNFLDs are CKD and hypertension. Conversely, RNFLDs can be an ocular feature in patients with CKD. Fundoscopy can help detect systemic diseases, and assessment for RNFLDs should be considered in CKD patients.

● **KEYWORDS:** chronic kidney disease; retinal nerve fiber layer defects; Kailuan Eye Study; fundus examination

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INTRODUCTION

Chronic kidney disease (CKD) is a medical term used to describe heterogeneous diseases with many causes. With the progressive deterioration in renal functioning, CKD can eventually progress to end-stage renal failure. The high prevalence and mortality rate of CKD are global health concerns. The prevalence of CKD is approximately 13.4% worldwide[1]. The prevalence of CKD in China has reached

10.8%, about 119.5 million people in China are currently afflicted with CKD[2].

The mortality rate of patients with CKD is very high due to various complications, including cardiovascular disease, anemia, cognitive decline, mineral deficiencies, bone disorders, even fractures[3]. In 2017, the number of deaths from CKD was 1.2 million, an increase of 41.5% from 1990[4]. By 2040, it is estimated that CKD will be the fifth largest cause of premature death globally[5]. The early detection of CKD can help prevent serious complications and alleviate illness burden. However, in the early stages, the symptoms of CKD are often difficult to detect[3].

Renal and retinal circulation share similar pathways of development, structural anatomy, physiological and pathological characteristics, and common risk factors for vascular dysfunction[6]. Accordingly, accumulating studies have demonstrated that the kidneys may exhibit similar relationships to the eye regarding structure and disease. An increased risk of retinal vascular disease (RVD) has been reported in patients with CKD[7]. The prevalence of major eye diseases and impaired vision in patients with CKD is increased two- to seven-fold times compared to patients without CKD[8]. Moreover, patients with CKD have lower thickness of peripapillary and parafoveal retinal nerve fiber layer (RNFL), peripapillary choroidal, and central macular[9-11]. Retinal microvascular caliber and fractal dimension can also be affected by kidney function[12].

RNFL defects (RNFLDs), caused by progressive axonal loss of ganglion cells, can lead to vision impairment and visual loss[13-14]. RNFLDs can be detected using fundus photography or optical coherence tomography, which is convenient and noninvasive. RNFLDs are not only considered early signs of glaucomatous optical damage[15] but also have significant association with other systemic conditions, such as diabetic retinopathy, arterial hypertension, stroke, cerebrovascular infarcts, and reduced renal function[16-22].

Since RNFLDs may be sequelae of retinal vascular insufficiency, we speculated that they are associated with CKD. However, scant attention has been paid to the relationship between CKD and RNFLDs unfolds hitherto. Accordingly, we aimed to gain further insight into the relationship between RNFLDs, CKD, and renal function in this large population-based study.

SUBJECTS AND METHODS

Ethical Approval The Kailuan Eye Study is a part of The Kailuan Study (registration number: ChiCTR-TNC1100148). The Beijing Tongren Hospital's Medical Ethics Committee authorized the clinical observational program, which was in line with the Helsinki Declaration. After the study's purpose, benefits, and possible consequences were explained, all participants completed informed consent forms.

Study Population Participants from the Kailuan Longitudinal Study participated in the Kailuan Eye Study. Employees, retirees, and their families from the Kailuan Group Company participated in the Kailuan Study, which is located in Tangshan City, Hebei Province, approximately 150 km southeast of Beijing. The study was conducted between 2006 and 2016. At baseline, in 2006, 101 510 participants in the cohort study (81 110 males; aged 18-98y) were examined repeatedly and prospectively every two years until 2016. We have comprehensively described the study design and inclusion/exclusion criteria in the previously published literature[23-24]. In the Kailuan cohort, 14 440 individuals participated in the Kailuan Eye Study by using cluster random sampling based on the examination unit.

General Information and Laboratory Measurements Interviews with a standardized questionnaire were conducted with all participants to collect their birth date, sex, known major systemic diseases, education level, family disease history, and variety of lifestyle variables (including consumption of alcohol and smoking, sleeping condition, and physical activity). Weight, height, and circumference of the waist and hip were also measured. Weight (kg) divided by the square of height (m^2) equals body mass index (BMI). After a 5-min rest, heart rate and blood pressure were measured on the right arm; blood pressure was assessed twice, at five minutes interval, and averaged.

We collected fasting blood and urine samples to determine fasting glucose, total bilirubin, total protein, albumin, urine protein, uric acid, urea, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, glutamate pyruvate transaminase, hypersensitive C-reactive protein, hemoglobin concentration, red blood, white blood, neutrophil, and blood platelet count.

Participants were diagnosed as having diabetes mellitus if the concentration of fasting serum glucose was ≥7.0 mmol/L or if they were currently using antidiabetic drugs; diagnostic criteria for hypertension was systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current antihypertensive treatment. Based on creatinine concentration, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used to calculate the estimated glomerular filtration rate (eGFR)[25]; and it was divided into different stages by values of eGFR. Stage 1 with renal disease, and eGFR is normal ≥90 mL/min·1.73 m^2. Stage 2 refers to eGFR at 60-89 mL/min·1.73 m^2. Stage 3 refers to eGFR at 30-59 mL/min·1.73 m^2, eGFR of stage 4 is 15-29 mL/min·1.73 m^2. CKD stage 5 is defined as an eGFR<15 mL/min·1.73 m^2.

Ocular Examination Comprehensive ophthalmic examinations were performed on all participants, including visual acuity (pin-hole visual acuity was added if necessary),

slit-lamp assisted anterior segment biomicroscopy and non-contact tonometry. Using a non-mydriatic fundus camera, two 45°color fundus photographs were centered on the macula and optic nerve head respectively (CR6-45NM; Canon Inc. Tokyo, Japan). If the pupil was too small to obtain a clear image, it was medically dilated with mydriatic eye drops. Other ocular biometry, including central corneal thickness, anterior chamber depth, eye axial length, lens thickness, and corneal diameter, were obtained using an optical biometer (Lenstar 900; Haag-Streit, Koeniz, Switzerland) on the right eye. For quality control, photographers and operators received training and certification from experienced ophthalmic operators and retinal specialists at the Beijing Tongren Eye Center.

Retinal Nerve Fiber Layer Defect Evaluation Based on the fundus photographs of each eye, RNFLDs were assessed anonymously without information regarding other ocular or systemic parameters. RNFLD severity was determined using the eye exhibiting a more severe condition, and we used the eye with a more severe status. The diagnosis of RNFLDs includes localized RNFLDs and diffuse RNFL atrophy. Localized RNFLDs were defined as wedge-shaped rather than spindle-shaped defects located within the healthy RNFL with a clear border and touching or close to the optic disc edge (Figure 1). The width of RNFLDs was more significant than that of the main retinal vessels. The definition of diffuse RNFLD was a diffuse loss or thinning of the RNFL with unclear boundaries, regardless of how wide the boundary was and when the bare capillaries could be seen clearly. Multiple RNFLDs were defined as two or more localized defects separated by normal nerve fibers (Figure 2).

Photographs were evaluated by two highly trained and experienced ophthalmologists (Wan QQ and Fang LJ). The reliability between the ophthalmologists was evaluated, and the kappa coefficients were calculated (P<0.001; kappa=0.897). If in doubt, a panel of three professional ophthalmologists (Wei WB, Wang YX, and Zhou JQ) would reevaluate the fundus photographs.

Exclusion Criteria Eyes with media opacities or tessellated myopic fundi that affected the observation of RNFL changes were excluded. Participants with high intraocular pressure or glaucoma were excluded. Participants lacking renal function tests were also excluded.

Statistical Analysis Mean, standard deviation and 95% confidence interval (CI) were calculated to express continuous variables. Percentages were calculated for categorical variables. Logistic regression models were performed to detect the risk factors for the prevalence of RNFLDs. The presence of RNFLDs was used as the dependent variable, whereas the potential risk factors for RNFLDs were used as independent variables. We excluded some factors due to the possible multicollinearity and lack of clinical significance. The statistical method for identifying risk factors for CKD was similar to the previous one used to identify RNFLDs. Odds ratio (ORs) and 95%CI were calculated and recorded. Statistical significance was defined as a P value <0.05. SPSS 24.0 (SPSS for windows, Chicago, IL, USA) was used for all statistical analysis.

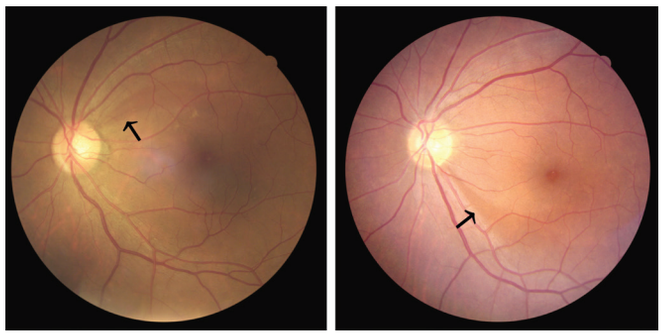

Figure 1 Localized retinal nerve fibre layer defect in color fundus photography (black arrow).

RESULTS

A total of 14 440 individuals (9835 males, 68.1%) underwent ophthalmology examinations. The mean age of all participants was 54.0±13.3y (range: 20-110y). Among all participants, 1933 were excluded due to missing clear fundus photographs or information on CKD status. A total of 12507 participants (8533 males, 68.23%) were finally included (mean age: 53.19±13.066y; range: 21-108y). Details of inclusion and exclusion were shown in Figure 3.

Risk Factors for Retinal Nerve Fiber Layer Defects RNFLDs were found in 621 participants, representing RNFLD prevalence of 5.0% (95%CI: 4.6%-5.34%). Of the 621 participants, 70 (11.27%) had multiple localized RNFLDs. Prevalence of RNFLDs and multiple RNFLDs of different CKD stages were shown in Figure 4. The most common location was the superior temporal region (53.44%), followed by the inferior temporal region (26.09%). The basic clinical characteristics of the study sample were shown in Table 1.

We compared participants with and without RNFLDs (Table 2). Before adjusting risk factors, the prevalence of RNFLDs was significantly associated with the severity of CKD. The ORs and 95%CI of CKD stage 3, stage 4 and stage 5 were 3.235 (2.497-4.19), 7.57 (4.607-12.44), and 15.928 (9.129-27.792), respectively. There still existed strong correlations between RNFLDs and CKD in the multiple analysis models we designed. In model 5, after adjusted all potential risk factors, the statistical results showed that the incidence of RNFLDs increased with the stage of CKD, the ORs of CKD stage 3, stage 4 and stage 5 were 1.698, 4.167, and 9.512 respectively.

Additionally, logistic regression analysis was used to examine the factors of multiple RNFLDs (Table 3). Before adjusting risk factors, the prevalence of RNFLDs was significantly associated

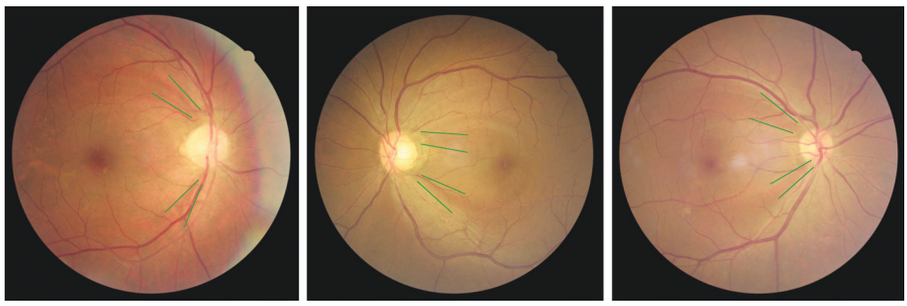

Figure 2 Multiple retinal nerve fiber layer defects in color fundus photography (green lines).

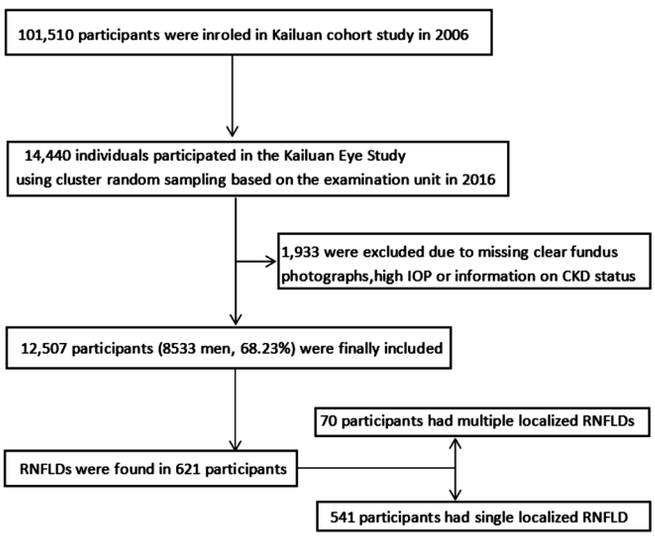

Figure 3 Flow chart of participants IOP: Intraocular pressure; CKD: Chronic kidney disease; RNFLD: Retinal nerve fiber layer defect.

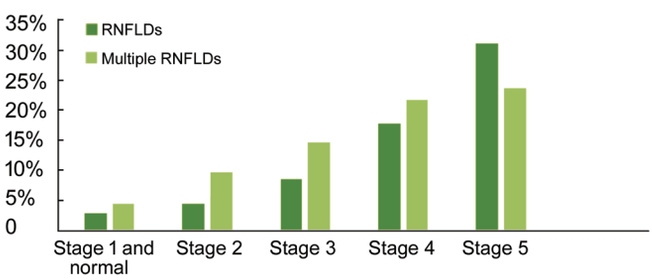

Figure 4 Prevalence of RNFLDs and multiple RNFLDs in different CKD stages CKD: Chronic kidney disease; RNFLD: Retinal nerve fiber layer defect.

with the severity of CKD. The ORs and 95%CI of CKD stage 3, stage 4 and stage 5 were 3.72 (1.257-11.012), 6.042 (1.476-24.73) and 6.797 (1.645-28.085), respectively. There still existed strong correlations between multiple RNFLDs and CKD in the multiple analysis models we designed. In model 3, after adjusted all potential risk factors, the statistical results show that the incidence of multiple RNFLDs increased with the stage of CKD, the ORs and 95%CI of CKD stage 3, and stage 5 were 4.465 (1.171-17.026) and 11.833 (2.237-62.602), respectively.

Risk Factors for Chronic Kidney Disease A total of 2294 participants had CKD (18.34%; 95%CI: 17.68-18.99). According to univariate analysis, CKD was more prevalent in participants with the following characteristics: males, older age, higher diastolic blood pressure, high heart rate, and high serum concentration of high-sensitivity C-reactive protein, high-density lipoprotein, low-density lipoprotein, total cholesterol, and total protein. In addition, patients with RNFLDs, heart failure, and diabetes mellitus might also experience the increased risk of CKD. In the subsequent multivariate logistic analysis, there were significant associations between high prevalence of CKD and old age (OR: 1.090; 95%CI: 1.081-1.098); male sex (OR: 0.321; 95%CI: 0.269-0.383); the presence of hypertension (OR: 1.467; 95%CI: 1.228-1.752); the presence of diabetes mellitus (OR: 1.238; 95%CI: 1.035-1.482); high serum concentration of total protein (OR: 1.023; 95%CI: 1.008-1.038); total cholesterol (OR: 1.443; 95%CI: 1.375-1.515), and high-sensitivity C-reactive protein (OR: 0.924; 95%CI: 0.897-0.951); high serum concentration of high-density lipoprotein (OR: 0.541; 95%CI: 0.436-0.67) and low-density lipoprotein (OR: 0.791; 95%CI: 0.712-0.878); and high heart rate (OR: 1.019; 95%CI: 1.013-1.026). The presence of RNFLDs (OR: 2.237; 95%CI: 1.683-2.972) were also risk factors for CKD (Table 4).

DISCUSSION

According to our cross-sectional, community-based study, 621 of 12 507 participants had RNFLDs, demonstrating an RNFLD prevalence of 5% (95%CI: 4.6%-5.34%). Furthermore, 2294 participants had CKD (18.34%; 95%CI: 17.68-18.99). RNFLDs were most commonly detected in the superior temporal region followed by the inferior temporal region. After adjusting for several risk factors, there remained a significant association between RNFLDs and CKD; the relationship between the presence of multiple RNFLDs and CKD was also significant, and the incidence of RNFLDs suggested an increasing with the stage of CKD. In contrast, an increased prevalence of CKD was associated with RNFLDs after adjusting for sex, age, diabetes mellitus and other risk factors.

In this extensive population-based study, we employed fundus photography to evaluate RNFLDs, as has been previously conducted in other research studies[26,17]. The prevalence of RNFLDs we reported is consistent with that reported previously. For instance, in a survey conducted by Na *et al*[17]

Table 1 Characteristics of the study sample

Variables	Total sample (*n*=12507)	Presence of RNFLDs				Characteristics of RNFLDs (*n*=621)			
		No (*n*=11886)	Yes (*n*=621)	χ^2/t	*P*	Single RNFLD (*n*=551)	Multiple RNFLDs (*n*=70)	χ^2/t	*P*
Age, y, mean (SD)	53.19 (13.066)	52.92 (13.138)	58.34 (10.335)	-12.555	<0.001[a]	58.2 (10.634)	59.47 (7.552)	-0.97	0.333[a]
Gender, *n* (%)				7.666	0.006[b]			0.241	0.624[b]
Males	8533 (68.23)	8078 (68.0)	455 (73.27)			402 (73)	53 (75.7)		
Females	3974 (31.8)	3808 (32.0)	166 (26.73)			149 (27)	17 (24.3)		
ACD, mm, mean (SD)	2.725 (0.451)	2.73 (0.447)	2.647 (0.521)	2.934	0.004[a]	2.643 (0.514)	2.683 (0.589)	-0.445	0.657[a]
AL, mm, mean (SD)	23.666 (1.4)	23.677 (1.384)	23.443 (1.68)	3.11	0.002[a]	23.445 (1.744)	23.425 (0.962)	0.069	0.945[a]
SBP, mm Hg, mean (SD)	137.426 (18.987)	136.96 (18.753)	146.291 (21.142)	-9.406	<0.001[a]	146.196 (22.976)	151.345 (22.607)	-1.602	0.11[a]
DBP, mm Hg, mean (SD)	79.954 (10.412)	79.822 (10.328)	82.455 (11.622)	-4.839	<0.001[a]	82.211 (11.546)	84.213 (12.115)	-1.23	0.219[a]
BMI, kg/m^2, mean (SD)	30.651 (9.698)	30.638 (9.669)	30.902 (10.253)	-0.578	0.563[a]	30.873 (10.58)	31.108 (7.625)	-0.165	0.869[a]
Heart rate, time/min, mean (SD)	75.56 (11.234)	75.51 (11.202)	76.59 (11.811)	-2.599	0.082[a]	76.54 (11.424)	76.91 (14.376)	-0.159	0.874[a]
Fasting blood glucose, mmol/L, mean (SD)	6.111 (2.414)	6.066 (2.34)	6.958 (3.423)	-5.681	<0.001[a]	6.974 (3.526)	6.86 (2.577)	0.238	0.812[a]
HDL-C, mmol/L, mean (SD)	1.536 (0.593)	1.537 (0.599)	1.527 (0.455)	0.344	0.731[a]	1.531 (0.454)	1.498 (0.462)	0.522	0.602[a]
LDL-C, mmol/L, mean (SD)	2.973 (0.946)	2.972 (0.955)	2.980 (0.756)	-0.172	0.863[a]	2.957 (0.748)	3.143 (0.803)	-1.77	0.077[a]
TG, mmol/L, mean (SD)	2.099 (2.014)	2.088 (1.963)	2.321 (2.809)	-1.802	0.072[a]	2.26 (2.911)	2.771 (1.859)	-1.302	0.194[a]
TC, mmol/L, mean (SD)	4.612 (2.085)	4.613 (2.105)	4.591 (1.675)	0.226	0.821[a]	4.618 (1.633)	4.391 (1.966)	0.84	0.404[a]
TP, mmol/L, mean (SD)	73.49 (14.40)	73.406 (13.134)	75.153 (29.962)	-1.217	0.224[a]	75.24 (31.897)	74.513 (5.111)	0.166	0.869[a]
Urinary protein, *n* (%)				42.154	<0.001[b]			0.21	0.647[b]
-	11872 (94.923)	11318 (95.221)	554 (89.211)			492 (89.292)	62 (88.571)		
±	194 (1.551)	176 (1.481)	18 (2.899)			14 (2.5)	4 (5.714)		
+	225 (1.80)	201 (1.691)	24 (3.865)			22 (3.993)	2 (2.857)		
++	124 (0.991)	111 (0.934)	13 (2.093)			12 (2.178)	1 (1.429)		
+++	92 (0.736)	80 (0.673)	12 (1.932)			11 (1.996)	1 (1.429)		
Hypertension, *n* (%)	4311 (34.469)	3999 (33.6)	312 (50.2)	71.971	<0.001[b]	267 (48.457)	45 (64.286)	6.224	0.013[b]
Diabetic mellitus, *n* (%)	1821 (14.56)	1654 (13.9)	167 (26.9)	79.887	<0.001[b]	144 (26.134)	23 (23.857)	1.428	0.232[b]
CKD stage, *n* (%)				175.816	<0.001[b]			12.686	<0.001[b]
Stage 1 and normal	3266 (26.223)	3175 (26.712)	91 (14.654)			87 (15.789)	4 (5.714)		
Stage 2	6947 (55.545)	6639 (55.856)	308 (49.597)			278 (50.454)	30 (42.857)		
Stage 3	2098 (16.775)	1920 (16.153)	178 (28.663)			152 (27.586)	26 (37.143)		
Stage 4	129 (1.031)	106 (0.892)	23 (3.704)			18 (3.267)	5 (7.143)		
Stage 5	67 (0.536)	46 (0.387)	21 (3.382)			16 (2.904)	5 (7.143)		

ACD: Anterior chamber depth; AL: Axial length; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TG: Triglyceride; TC: Total cholesterol; TP: Total protein; CKD: Chronic kidney disease; RNFLD: Retinal nerve fiber layer defect. *P* value have not been adjusted for multiple testing. [a]Independent *t*-test; [b]χ^2 test.

Table 2 Logistic regression analysis for the related risk factors of the presence of RNFLDs in the Kailuan Eye Study

Risk factors	β	Odds ratio (95%CI)	*P*
Model 1			
CKD			
CKD stage 3	1.174	3.235 (2.497-4.190)	<0.001
CKD stage 4	2.024	7.57 (4.607-12.44)	<0.001
CKD stage 5	2.768	15.928 (9.129-27.792)	<0.001
Model 2			
CKD			
CKD stage 3	0.821	2.272 (1.713-3.013)	<0.001
CKD stage 4	1.690	5.420 (3.262-9.007)	<0.001
CKD stage 5	2.513	12.336 (6.988-21.779)	<0.001
Age	0.025	1.026 (1.018-1.033)	<0.001
Gender	0.304	1.356 (1.126-1.632)	0.001
Model 3			
CKD			
CKD stage 3	0.693	2.000 (1.333-3.001)	0.001
CKD stage 4	1.639	5.149 (2.616-10.136)	<0.001
CKD stage 5	2.446	11.538 (5.388-24.706)	<0.001
Age	0.021	1.021 (1.01-1.033)	<0.001
Gender	0.263	1.301 (0.976-1.735)	0.073
Diabetic mellitus	0.477	1.611 (1.259-2.06)	<0.001
Hypertension	0.454	1.574 (1.223-2.025)	<0.001
Model 4			
CKD			
CKD stage 3	0.744	2.104 (1.443-3.068)	<0.001
CKD stage 4	1.426	4.163 (1.943-8.919)	<0.001
CKD stage 5	2.115	8.289 (4.056-16.941)	<0.001
Age	0.028	1.028 (1.019-1.037)	<0.001
Gender	0.360	1.433 (1.13-1.818)	0.003
Model 5			
CKD			
CKD stage 3	0.529	1.698 (1.087-2.651)	0.02
CKD stage 4	1.427	4.167 (1.701-10.205)	0.002
CKD stage 5	2.253	9.512 (4.363-20.739)	<0.001
Age	0.025	1.025 (1.013-1.037)	<0.001
Gender	0.253	1.288 (0.977-1.70)	0.073
Diabetic mellitus	0.511	1.667 (1.265-2.197)	<0.001
Hypertension	0.325	1.385 (1.054-1.819)	0.019

Model 1: Not adjusted; Model 2: Adjusted for age and gender; Model 3: Adjusted for age, gender, triglyceride, heart rate, diabetic mellitus and hypertension; Model 4: Adjusted for age, gender, anterior chamber depth and axial length; Model 5: Adjusted for Model 4 and diabetic mellitus, hypertension and triglyceride. CI: Confidence interval; CKD: Chronic kidney disease; RNFLD: Retinal nerve fiber layer defect.

in Korea found that the estimated prevalence of RNFLDs was 4.8% (95%CI: 4.4%-5.3%) among 28 637 participants aged ≥19y. However, in the Beijing Eye Study[27], which enrolled 3242 participants aged ≥50y, the estimated prevalence of localized RNFLD was 14.8%, which was higher than the prevalence found in our study population; this discrepancy may be related to the differences in screening methods, characteristics of participants, and study designs. In patients with glaucoma, the most common site of RNFLDs is the inferior temporal region, whereas RNFLDs of the superior temporal region are closely associated with hypertension and diabetes[18,28]. Our findings are partly concordant with the previous investigation. It can be speculated that RNFLDs caused by systemic vascular factors often occur in the superior

Table 3 Logistic regression analysis for the related risk factors of multiple RNFLDs and in the Kailuan Eye Study

Risk factors	β	Odds ratio (95%CI)	*P*
Model 1			
CKD			
CKD stage 3	1.314	3.72 (1.257-11.012)	0.018
CKD stage 4	1.799	6.042 (1.476-24.73)	0.012
CKD stage 5	1.916	6.797 (1.645-28.085)	0.008
Model 2			
CKD			
CKD stage 3	1.228	3.416 (1.149-10.156)	0.027
CKD stage 4	1.699	5.468 (1.326-22.55)	0.019
CKD stage 5	1.839	6.288 (1.511-26.268)	0.011
Hypertension	0.565	1.759 (1.042-2.968)	0.034
Model 3			
CKD			
CKD stage 3	1.496	4.465 (1.171-17.026)	0.028
CKD stage 4	1.085	2.958 (0.274-31.910)	0.371
CKD stage 5	2.471	11.833 (2.237-62.602)	0.004

CI: Confidence interval; CKD: Chronic kidney disease; RNFLD: Retinal nerve fiber layer defect. Model 1: Adjusted for age and gender; Model 2: Adjusted for age, gender, diabetic mellitus and hypertension; Model 3: Adjusted for Model 2, anterior chamber depth and axial length.

Table 4 Multivariate logistic regression analysis for the related risk factors of the presence of CKD in the Kailuan Eye Study

Risk factors	β	Odds ratio (95%CI)	*P*
Age	0.086	1.090 (1.081-1.098)	<0.001
Sex	−1.137	0.321 (0.269-0.383)	<0.001
RNFLDs	0.805	2.237 (1.683-2.972)	<0.001
Hypertension	0.383	1.467 (1.228-1.752)	<0.001
Diabetes mellitus	0.214	1.238 (1.035-1.482)	0.019
Total cholesterol	0.367	1.443 (1.375-1.515)	<0.001
hs-CRP	−0.079	0.924 (0.897-0.951)	<0.001
Total protein	0.023	1.023 (1.008-1.038)	0.002
Heart rate	0.019	1.019 (1.013-1.026)	<0.001
HDL-C	−0.615	0.541 (0.436-0.67)	<0.001
LDL-C	−0.235	0.791 (0.712-0.878)	<0.001

CI: Confidence interval; RNFLD: Retinal nerve fiber layer defect; CKD: Chronic kidney disease; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; hs-CRP: High-sensitivity C-reactive protein.

temporal region, whereas RNFLDs caused by glaucoma often happen in the inferior temporal region, indicating that the two types of RNFLDs might have different pathogeneses and clinical manifestations. RNFLDs caused by a microvascular abnormality or vascular imbalance is more prevalent on the superior side because of the gravitational influence[29].

We also found that presence of multiple RNFLDs were strongly associated with CKD and hypertension, which is in line with the findings of earlier studies[16,22] supporting the hypothesis that RNFLDs could be considered potential biomarkers of systemic vascular diseases. In 1992, Chihara and Honda[30] found multiple RNFLDs in patients with glaucoma, and multiple RNFLDs were identified as localized RNFLDs separated by normal retinal structures, which were correlated with myopia and small optic disc. Still, they did not strongly correlate with intraocular pressure. According to these findings, vascular factors contribute to RNFLDs development. In a study conducted by Jung *et al*[16] a significant correlation between multiple RNFL defects and systemic diseases, including cerebrovascular disease, hypertension, and end-stage renal disease was noted. Additionally, another investigation conducted by Shin *et al*[22], revealed that an increasing number of RNFLDs was significantly associated with younger age, higher glycated hemoglobin, higher mean 24-h systolic blood pressure, and lower eGFR. Our study confirmed that multiple RNFLDs were more closely related to vascular factors than

glaucoma; therefore, we hypothesized that CKD effects on microvasculature and damage to the nervous system contribute to RNFLDs.

Conversely, we also found that CKD strongly correlated with RNFLDs after adjusting for confounding risk factors. Previous studies have confirmed the effects of CKD on the eyes, but there needs to be more consensus among different investigations. In previous studies, participants with CKD were more likely to be with vision impairment and major eye diseases, especially retinopathy, than those without CKD[8,31-32]. In a large population-based study conducted by Lin *et al*[7], patients with CKD had a high risk of retinal vascular disease. Retinal vascular signs can be prognostic factors for CKD[33]. Additionally, CKD led to retinal thinning; eGFR was positively correlated with choroidal thickness[11]. In an investigation conducted by Wu *et al*[10], patients with CKD showed significantly reduced macular thickness and retinal neural impairment compared with the control group. In contrast, intraocular pressure was not associated with neurological impairment in patients with CKD. Therefore, CKD may affect the retina's microvascular function and reduce retinal ganglion cell activity. The thickness of the nerve fiber layer around the optic papilla is found to be reduced in individuals with decreased renal function, according to several studies[34-36]. Using optical coherence tomography, Zhuang *et al*[37] studied correlations between the level of eGFR and degree of retinal perfusion injury; notably, vascular density in the superficial vascular complex decreased significantly compared with that in the deep vascular complex with deteriorating kidney function. Accordingly, CKD exhibited a greater effect on the superficial retina than the deep retina. In a survey conducted by Majithia *et al*[31], the researchers discovered a significant correlation between CKD and compromised renal function with the thinning of ganglion cell-inner plexiform layer and RNFL in both Asian and caucasian eyes. Based on previous research, we investigated correlations between RNFLDs and CKD in the present study and found a positive association.

Studies have investigated the influencing factors and potential mechanisms of RNFLDs. Approximately 50 years ago, RNFLDs were identified as an important feature in the early diagnosis of glaucoma. It was assumed that RNFLDs were not only a sign of glaucoma but could also be associated with other factors. In rhesus monkey, Hayreh and Jonas[38] found that chronic arterial hypertension and atherosclerosis contribute to localized RNFLDs, but the neuroretinal rim did not decrease. During the course of clinical trials involving human subjects, Shin *et al*[22] reported a 1.13-fold increase in the probability of developing RNFLDs for every 10 mm Hg increases in blood pressure. Additionally, compared with retinal microvascular abnormalities, the OR between localized RNFLDs and systemic hypertension was higher than that between microvascular abnormalities with systemic hypertension[39], suggesting that the diagnostic specificity of localized RNFLDs was much higher than that of microvascular abnormalities and that diabetes mellitus may also lead to the development of localized RNFLDs[20]. Nevertheless, it has also been reported that optic nerve head cupping did not increase with the severity of the disease classification in diabetes[18]. In addition, RNFLD presence is significantly associated with male sex and older age[17]; this was confirmed in the present study.

Several factors may contribute to these observed changes. One might be the common pathogenesis and risk profile underlying CKD and eye diseases: some common vascular risk factors among CKD and retina vascular disease, including aging, hypertension, diabetes, smoking, and obesity[40]. Moreover, the glomerular vascular network and retinal circulation share structural similarities, and there are other similarities between physiological and pathological characteristics[41]. Pathophysiological similarities between the glomerular vascular network and retinal circulation include oxidative stress, inflammation, endothelial dysfunction, and microvascular changes, which can result from advanced glycation end-product accumulation[42-44].

Furthermore, the chronic hypoxia theory suggests that loss of microvasculature may be the reason of increased hypoxia. Retinal arterial diameter narrows[45], and fluctuations in blood pressure caused by CKD and focal infarction of the RNFL lead to the formation of retinal cotton wool spots, which are considered as a manifestation of RNFL axoplasmic accumulation, resulting in RNFLDs. This phenomenon may reflect underlying systemic microvascular damage and indicate potential kidney function injury[12,46]. In addition, patients with CKD were frequently afflicted with several major neurological complications, such as cerebrovascular disease, cerebral cortical thinning, cognitive impairment, dementia, and peripheral neuropathy[47-48]. As the eye and brain share similar embryological origins and physiological properties, and the retina is also considered the terminal part of the central nervous system, neuronal damage of the central nervous system may lead to retinal ganglion cells damage[49-50]. Therefore, this supports speculation that CKD may also contribute to the progress of RNFLDs.

However, the limitations of our study should also be addressed. First, the causal associations cannot be appropriately distinguished in this cross-sectional study. Second, selection bias cannot be excluded. The study was based on a community sample, most participants were young adults, the presence of age-related diseases was significantly lower, and the generalization of the results to other populations is limited. Third, participants with high intraocular pressure were

excluded; the history of glaucoma was not investigated in detail. These missing variables may have biased estimates of risk factors. Fourth, we assessed the presence of RNFLDs using fundus photographs, and the results might have included subjective errors, thereby creating uncertainty in the prevalence of RNFLDs. Fifth, using serum creatinine as a single indicator of kidney function may lead to an incomplete evaluation, because most patients with CKD might have average serum creatinine concentration after receiving therapy. Despite these limitations, the study also demonstrated some strengths, such as the large sample size, detailed questionnaire survey, comprehensive laboratory examinations, and standardized imaging data. As the first study to evaluate the association between CKD and RNFLDs in a relatively large sample, the observations may be valuable for future investigations.

In conclusion, according to this Chinese population-based cross-sectional study, CKD is a systemic microvascular disease that shares similar risk factors with retinal disease, which leads to an increased incidence of RNFLDs and multiple RNFLDs. When physicians evaluate a patient with RNFLDs, systemic vascular risk, especially CKD, should be considered and a routine fundus examination should be conducted.

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