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Retinal Arteriolar Narrowing and Subsequent Development of CKD Stage 3: The Multi-Ethnic Study of Atherosclerosis (MESA)

Joanne Wen Yee Yau, BMedSci, MBBS (Hons)¹, Jing Xie, PhD¹, Ryo Kawasaki, MD, PhD¹, Holly Kramer, PhD², Michael Shlipak, MD³, Ronald Klein, MD, MPH⁴, Barbara Klein, MD, MPH⁴, Mary Frances Cotch, PhD⁵, and Tien Yin Wong, MBBS, PhD^{1,6}

¹Centre for Eye Research Australia, The Royal Victorian Eye and Ear Hospital, University of Melbourne, Victoria, Australia

²Department of Preventive Medicine, Loyola Medical Center, San Francisco, CA

³Veterans Affairs Medical Center, University of California, San Francisco, San Francisco, CA

⁴Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison, WI

⁵Division of Epidemiology and Clinical Applications, National Eye Institute, National Institutes of Health, Bethesda, MD

⁶Singapore Eye Research Institute, Singapore National Eye Centre, Singapore

Abstract

Background—Microvascular disease is a major pathogenic factor for chronic kidney disease (CKD) in persons with diabetes, but the role of microvascular disease in the development of CKD in the general population is unclear. The aim of this study is to examine whether microvascular disease precedes the development of CKD stage 3 in participants of the Multi-Ethnic Study of Atherosclerosis (MESA).

Study Design—Population-based cohort study.

Setting & Participants—MESA is a prospective cohort study of adults aged 45–84 years living in 6 US communities; 4,594 adults with estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m² when they underwent retinal photography (visit 2: in 2002–2004) were examined.

Predictor—Retinal microvascular caliber measured from fundus photographs.

Outcomes—Incident CKD stage 3 (ie, eGFR < 60 mL/min/1.73 m²) at 2 subsequent follow-up examinations (visit 3 in 2004–2005, and visit 4 in 2005–2007) and an annual eGFR decrease > 1 mL/min/1.73 m² computed using the CKD Epidemiology Collaboration (CKD-EPI) equation.

Results—After a median follow-up of 4.8 years, there were 232 incident CKD stage 3 cases. Overall, retinal microvascular caliber was not associated with incident CKD stage 3. However, in race-stratified analysis, narrower arterioles in whites was associated with a higher risk of developing CKD stage 3 after adjusting for age, sex, blood pressure, diabetes, and other factors (HR, 1.78; 95% CI, 1.01–3.15; $P = 0.04$, lowest vs highest arteriolar caliber tertile). This association was seen even in whites without hypertension and diabetes (HR, 2.95; 95% CI, 1.10–7.98; $P = 0.03$). Retinal arteriolar caliber was not associated with incident CKD stage 3 in African Americans, Chinese, or Hispanics.

Address correspondence to Joanne Wen Yee Yau, MBBS (Hons), Centre for Eye Research Australia, University of Melbourne, 32 Gisborne St, East Melbourne 3002, Victoria, Australia. jwyau@unimelb.edu.au.

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Limitations—Analyses were based on a single eGFR measurement, and retinal microvascular caliber and eGFR measurements were not ascertained concurrently.

Conclusion—Microvascular changes as manifest in the eye may contribute to the development of CKD stage 3 in whites.

INDEX WORDS

Microvascular changes; retinal microvascular caliber; chronic kidney disease

Chronic kidney disease (CKD) is a significant health problem affecting more than 20 million persons in the United States alone.¹ Although microvascular disease is a major pathogenic risk factor for CKD in persons with diabetes, the contribution of microvascular processes to CKD development in the general population is unclear.²⁻⁵

The retinal and renal circulations share homologous anatomic, physiologic, and pathologic characteristics.^{6,7} Hence, assessment of the retinal microvasculature may offer the opportunity to examine early microcirculatory changes associated with the development of CKD.

Two previous longitudinal studies, both conducted in diabetic populations, have suggested an association between retinal microvascular caliber and incident CKD.^{8,9} However, prospective data from the general population presently are unavailable. To address this gap, we examined the association of retinal microvascular caliber with incident CKD stage 3 in a diverse multiethnic population-based cohort.

METHODS

Study Population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study of 6,814 men and women aged 45-84 years without a history of clinical cardiovascular disease living in 6 US communities. The main objective of this study was to identify risk factors for subclinical and clinical cardiovascular disease progression. Detailed methods of MESA have been described previously.¹⁰ In brief, 6,814 participants composed of whites, African Americans, Hispanics, and Chinese were recruited between July 2000 and July 2002 from Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; New York City, NY; and St Paul, MN.

Of the original cohort of 6,814 participants, 4,594 (67.4%) with an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m² at baseline (visit 1) who had gradable retinal photographs at visit 2 (2002-2004) and creatinine data at subsequent follow-up examinations (visit 3 in 2004-2005, and visit 4 in 2005-2007) were included in this analysis.

The tenets of the Declaration of Helsinki were followed and institutional review board approval was granted at all MESA sites. Written informed consent was obtained from each participant.

Retinal Photography and Measurement of Baseline Retinal Vascular Caliber

Retinal photography was performed at visit 2 using a standardized protocol.¹¹ In brief, participants had both eyes photographed with a 45° 6.3-megapixel digital nonmydriatic camera in a darkened room. Two photographic fields were obtained for each eye, one centered on the optic disk and the other centered on the fovea. All images were evaluated by trained graders masked to patients' characteristics at the University of Wisconsin, Madison.

Retinal microvascular caliber was measured using a computer-based program (IVAN, University of Wisconsin, Madison) based on a detailed protocol.¹² Optic-disc-centered right-eye photographs were selected for measurement; the left-eye photograph was used if retinal vascular caliber could not be measured in the right eye. For each photograph, all arterioles and venules coursing through an area 0.5-1 disc diameter from the optic disc margin were measured and the biggest 6 arteriolar and venular calibers were summarized as the central retinal artery equivalent (CRAE) and central retinal venular equivalent (CRVE) based on the Knudtson formula.¹³ Reproducibility of these measurements has been reported, with intra- and intergrader intraclass correlation coefficients ranging from 0.78-0.99.¹²

Retinopathy signs were graded in both eyes as previously described.¹¹ Retinopathy was considered to be present if any characteristic lesions as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS)¹⁴ severity scale was present: microaneurysms, hemorrhages, cotton wool spots, intraretinal microvascular abnormalities, hard exudates, venous beading, and new vessels. These lesions were defined as present if graded as either definite or probable.

Ascertainment of Incident CKD Stage 3

Serum creatinine was measured from blood samples collected at baseline, visit 3, and visit 4 examinations. We calculated eGFR using the CKD Epidemiology Collaboration (CKD-EPI) equation.¹⁵ Incident CKD stage 3 was defined as the development of eGFR <60 mL/min/1.73 m² at visit 3 and 4 plus an annual decrease in eGFR >1 mL/min/1.73 m².

Assessment of Other Risk Factors

All participants underwent an extensive interview, physical examination, and laboratory investigation at each follow-up examination. Information for medication use, cigarette smoking status, and alcohol consumption were self-reported.¹⁰ Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or current use of antihypertensive medications. Diabetes mellitus was defined as fasting plasma glucose level ≥ 126 mg/dL (≥ 7.0 mmol/L) or use of insulin or oral hypoglycemic medication. Height and weight were measured to determine body mass index. Fasting (>12 hours) blood samples were drawn from participants and analyzed for serum glucose, hemoglobin A_{1c}, plasma total and high-density lipoprotein cholesterol, and triglycerides. Low-density lipoprotein cholesterol was calculated using the Friedewald equation.¹⁶

Statistical Analysis

Study participants were censored if they did not have eGFR <60 mL/min/1.73 m² by the time of their last study visit at examination 4. The relationship between baseline retinal microvascular caliber and incident CKD stage 3 was examined using Kaplan-Meier survival estimates and a Cox proportional hazards regression model after adjusting for potential confounders. We constructed 3 models: model 1 initially adjusted for age, sex, study center, and tertiles of CRAE in models of CRVE and vice versa; model 2 included additional adjustments for systolic blood pressure, antihypertensive medications, body mass index, triglyceride level, smoking status, fasting glucose level, hemoglobin A_{1c} level, and log albumin-creatinine ratio; and model 3 was adjusted for all variables in model 2 plus the presence of any retinopathy. We also tested for interaction between risk factors. Because there was a significant interaction with ethnicity ($P = 0.03$), we performed stratified analysis by ethnicity. Finally, we also performed supplementary analyses by stratifying the population according to diabetes and hypertension status.

RESULTS

Table 1 lists baseline characteristics according to incident CKD stage 3 status, and Tables 2 and 3 list baseline characteristics of participants stratified by retinal arteriolar and venular caliber tertiles. In general, participants who developed CKD stage 3 were older and more likely to be white, women, and current smokers and have hypertension, diabetes, and increased triglyceride levels.

After a median follow up of 4.8 (range, 1.1-6.6) years, 232 (5.1%) participants developed CKD stage 3 (annual incidence rate, 1.1%). As listed in Table 4, retinal vascular caliber was not associated with incident CKD stage 3 in all MESA participants.

In race-specific subgroup analysis, whites with narrower CRAE had a higher risk of incident CKD stage 3 compared with those with a wider CRAE (Table 5). After adjusting for age, sex, systolic blood pressure, and other risk factors, whites with narrower CRAE were more likely to have eGFR <60 mL/min/1.73 m² (hazard ratio, 1.78; 95% confidence interval, 1.01- 3.15; *P* = 0.04, lowest vs highest arteriolar caliber tertile). There were no significant associations of CRAE or CRVE with incident CKD stage 3 in African Americans, Chinese, or Hispanics.

Whites with the narrowest CRAE tertile who did not have diabetes and hypertension also were more likely to have eGFR <60 mL/min/1.73 m² (hazard ratio, 2.95; 95% confidence interval, 1.10-7.98; *P* = 0.03; Table 6). There was insufficient power to evaluate the relationship in participants with diabetes or hypertension (data not shown).

DISCUSSION

In this large prospective multiethnic cohort study of middle-aged persons with eGFR ≥60 mL/min/1.73 m² at baseline, we found no overall associations between retinal microvascular caliber and incident CKD stage 3 in all MESA participants. However, in race-stratified analysis, white adults with narrower retinal arterioles were more likely to develop incident CKD stage 3 during the ensuing 4.8 years compared with those with wider retinal arterioles, independent of known risk factors. This association was not present in African Americans, Chinese, or Hispanics. Furthermore, in whites without diabetes and hypertension, presumably those at lower risk of CKD, narrower arterioles also were associated with a nearly 3-fold higher risk of CKD stage 3, suggesting that risk of CKD stage 3 in whites may be related to microvascular mechanisms beyond the effects of diabetes and hypertension.

To our knowledge, our study provides the first prospective data for the relationship between retinal microvascular caliber and incident CKD stage 3 in the general population. Previous studies have examined this relationship in either cross-sectional studies or persons with diabetes. In the Atherosclerosis Risk in Communities (ARIC) Study, middle-aged persons with narrower CRAE and CRVE were more likely to have a decrease in kidney function.¹⁷ A Danish study of persons with type 1 diabetes showed that individuals with narrower CRAE were more likely to have nephropathy,¹⁸ and similar cross-sectional findings were reported in Asian populations.^{19,20} In contrast, the Cardiovascular Health Study (CHS) showed that retinal microvascular caliber was not associated with kidney function decrease²¹; however, selection and survival bias were thought to have masked any associations in these elderly people. In the only prospective study to date of white individuals with diabetes from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), narrower CRAE was cross-sectionally associated with proteinuria,²² but larger CRVE was associated with a higher incidence of CKD in those with type 1⁸ and type 2 diabetes,⁹ respectively. In contrast, our study of the general population did not find an overall association. Instead, we showed that narrower CRAE was associated with incident

CKD stage 3 in only whites. Several reasons may account for this different finding. First, there were much fewer diabetic participants in MESA compared with the WESDR, a cohort containing only participants with diabetes. It is possible that microangiopathic processes may be less important for the development of CKD stage 3 in the general nondiabetic population, resulting in our overall null association. Second, the effect of interethnic variation could have altered, obscured, or attenuated any underlying associations. Therefore, results of MESA may not be directly comparable to those for a predominantly white population. Last, it also is possible that the creatinine-based eGFR formula may be inaccurate for the diagnosis of eGFR <60 mL/min/1.73 m² in nonwhite individuals, resulting in systematic misclassification of CKD stage 3 and attenuation of any true underlying associations.²³

Reason(s) for this possible racial/ethnic variation in retinal microvascular caliber association with CKD stage 3 risk are unclear, but we speculate the following. First, there may be biological processes (including genetic factors) that predispose the kidney to microvascular injury in certain racial/ethnic groups. Second, the relative contributions of major risk factors (eg, hypertension and obesity) to CKD pathogenesis vary among different racial/ethnic groups.^{24,25} However, these findings should be interpreted with caution because of the decreased sample sizes in our ethnic/racial subanalyses. Further studies are needed to verify these findings, and if such associations are validated, research that explores the reasons for these observed variations may offer new insights into the pathogenesis of CKD.

Narrowing of the retinal arterioles may reflect coexistent small-vessel damage in the kidney leading to subsequent impairment in kidney function. Experimental data from kidney biopsies of persons with type 1 diabetes have shown that narrower CRAE is morphologically related to extracellular matrix accumulation,²⁶ which is the principal pathologic process leading to diabetic nephropathy.²⁷ This mesangial expansion is thought to decrease glomerular filtration surface density, leading ultimately to eGFR decreases.²⁸ Histopathologically, retinal arteriolar narrowing reflects intimal thickening, medial hyperplasia, hyalinization, and sclerosis, changes that represent a microvascular response to chronically increased blood pressure.^{29,30} These same adverse mechanisms likely are occurring in the renal microvasculature; therefore, retinal arteriolar narrowing may forecast a decrease in kidney function. The association of endothelial dysfunction with retinal arteriolar narrowing also suggests that the relationship between retinal arteriolar narrowing and incident CKD may be mediated in part by systemic endothelial dysfunction.³¹ Furthermore, because smaller retinal arterioles have been shown to be markers of microvascular damage related to obesity,³² alcohol consumption,³² smoking,³² and inflammation,³³ it is plausible that these processes also may provide a common pathophysiologic link for the decrease in GFR.

The strengths of our study include a large population-based sample, a multiethnic cohort that enabled examination of ethnic differences, and quantitative and masked assessment of retinal microvascular caliber. Potential limitations include its relatively short follow-up, limited power in subgroup analyses, and lack of concurrent retinal photography and eGFR measurements. Serum creatinine and eGFR levels were determined from the first examination, whereas retinal vessel data were available from only the second examination. However, we believe that retinal images from the second examination are stable enough to be an excellent representation of the retinal vasculature at the time of the MESA baseline visit. Additionally, using a single eGFR measurement at baseline to determine whether participants were above or below the CKD stage 3 threshold of 60 mL/min/1.73 m² has limited precision and may result in misclassification of CKD status. For example, factors affecting renal hemodynamics, such as state of hydration, medications, and dietary protein intake, may result in falsely increased eGFR values and overestimation of the incidence of

CKD compared with multiple measurements over time. However, use of eGFR values from 2 consecutive follow-up visits in addition to an annual decrease $>1 \text{ mL/min/1.73 m}^2$ decreases misclassification of incident CKD stage 3 cases caused by random analytic variability.

In conclusion, we show that retinal arteriolar narrowing predicts risk of CKD stage 3 in whites, even those without diabetes and hypertension. This finding suggests that microvascular processes may have a role in CKD development in whites. Further research to validate these findings is warranted.

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Table 1

Baseline Characteristics of Study Population Comparing Those That Did and Did Not Develop CKD Stage 3

Characteristics	Incident CKD Stage 3		P
	No (n = 4,362)	Yes (n = 232)	
Men	2,097 (48.1)	95 (40.1)	0.03
Race			0.006
White	1,717 (39.4)	113 (48.7)	
Chinese American	515 (11.8)	17 (7.3)	
African American	1,173 (26.9)	65 (28)	
Hispanic	957 (21.9)	37 (16)	
Smoking status			0.006
Nonsmoker	2,150 (49.6)	115 (49.6)	
Ex-smoker	1,663 (38.3)	104 (44.8)	
Current	525 (12.1)	13 (5.6)	
Alcohol consumption			0.1
Never	823 (18.9)	50 (21.7)	
Former	962 (22.2)	60 (26.1)	
Current	2,556 (58.9)	120 (52.2)	
Hypertension	1,676 (38.4)	150 (64.7)	<0.001
Antihypertensive medication ^a	1,361 (31.2)	138 (59.5)	<0.001
ACE-inhibitor use	422 (9.7)	55 (23.7)	<0.001
Lipid-lowering medication	619 (14.2)	50 (21.6)	0.002
Diabetes mellitus	442 (10.1)	47 (20.3)	<0.001
Use of diabetes medications	347 (8)	40 (17.3)	<0.001
Age (y)	59 (52, 67)	69 (63, 73)	<0.001
Systolic blood pressure (mm Hg)	120.5 (109.0, 136.5)	133.2 (118.3, 146.5)	<0.001
Diastolic blood pressure (mm Hg)	72 (65.0, 78.5)	70.5 (64.5, 77.5)	0.5
Fasting plasma glucose (mg/dL)	89 (82, 97)	92 (84, 104)	<0.001
Total cholesterol (mg/L)	192 (171, 215)	194 (172, 217)	0.9
HDL cholesterol (mg/dL)	48 (40, 59)	49 (41, 59)	0.6
LDL cholesterol (mg/dL)	117 (96, 136)	115 (95, 135)	0.4
Triglycerides (mg/dL)	109 (77, 158)	123 (86, 170)	0.04
Body mass index (kg/m ²)	27.6 (24.5, 31.1)	27.8 (25.5, 31.8)	0.2
Diabetes duration (y)	4 (0, 9)	5 (0, 12)	0.2
Hemoglobin A _{1c} (%)	5.5 (5.2, 5.8)	5.5 (5.3, 6.0)	0.001
C-Reactive protein (mg/L)	1.8 (0.79, 4.12)	2 (0.94, 4.57)	0.3
Urinary albumin (mg/dL)	0.6 (0.3, 1.1)	0.6 (0.3, 1.1)	<0.001
Urinary creatinine (mg/dL)	111.8 (61.7, 167.0)	95.5 (50.7, 142.0)	<0.001
Urinary albumin-creatinine ratio	4.9 (3.2, 9.0)	5 (3.2, 9.4)	<0.001
eGFR _{CKD-EPI} (mL/min/1.73 m ²)			
Examination 1	83.5 (73.7, 93.3)	68.9 (65.2, 75.3)	<0.001
Examination 3	80.9 (71.3, 90.6)	57.4 (53.0, 59.5)	<0.001

Characteristics	Incident CKD Stage 3		<i>P</i>
	No (n = 4,362)	Yes (n = 232)	
Examination 4	77.6 (68.1, 88.1)	52.0 (46.2, 55.7)	<0.001

Note: N = 4,954. Categorical variables are given as number (percentage); continuous variables are shown as median (25th, 75th percentile).

Conversion factors for units: cholesterol in mg/dL to mmol/L, $\times 0.02586$; triglycerides in mg/dL to mmol/L, $\times 0.01129$; eGFR in mL/min/1.73 m² to mL/s/1.73 m², $\times 0.01667$.

Abbreviations and definitions: ACE, angiotensin-converting enzyme; CKD, chronic kidney disease; eGFR_{CKD-EPI}, estimated glomerular filtration rate using the CKD Epidemiology Collaboration equation; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

^aIn those with hypertension.

Table 2

Baseline Characteristics of Participants Stratified by Retinal Arteriolar Caliber Tertiles

	CRAE			<i>P</i>
	Lowest Tertile	Middle Tertile	Highest Tertile	
Men	796 (53.9)	760 (49.3)	636 (40.4)	<0.001
Race				<0.001
White	657 (44.5)	622 (40.3)	551 (35.0)	
Chinese American	173 (11.7)	181 (11.7)	178 (11.3)	
African American	364 (24.6)	422 (27.4)	452 (28.7)	
Hispanic	283 (19.2)	318 (20.6)	393 (25.0)	
Hypertension	719 (48.7)	601 (39.0)	506 (32.2)	<0.001
Antihypertensive treatment ^b	607 (43.1)	572 (38.7)	500 (33.0)	<0.001
ACE-inhibitor use	168 (11.4)	165 (10.7)	144 (9.2)	0.1
Lipid-lowering medication	201 (13.6)	245 (15.9)	223 (14.2)	0.2
Family history of diabetes ^b	210 (14.3)	217 (14.1)	227 (14.5)	0.9
Smoking status				<0.001
Nonsmoker	738 (50.2)	775 (50.5)	752 (48.1)	
Ex-smoker	607 (41.3)	593 (38.7)	567 (36.2)	
Current	126 (8.6)	166 (10.8)	246 (15.7)	
Age (y)	62 (54, 69)	59 (52, 67)	57 (51, 66)	<0.001
Systolic blood pressure (mm Hg)	127.5 (115.5, 141.5)	120.0 (110.0, 136.5)	116.5 (105.5, 132.5)	<0.001
Diastolic blood pressure (mm Hg)	74.5 (67.0, 81.5)	72.0 (65.5, 78.0)	69.5 (62.5, 75.5)	<0.001
BMI (kg/m ²)	27.7 (24.7, 31.1)	27.5 (34.4, 31.0)	27.7 (24.6, 31.3)	0.7
Physical activity (MET-min/wk) ^a	960.0 (262.5, 2,235.0)	787.5 (105, 1,892.5)	840 (157.5, 2,100.0)	0.01
Fasting plasma glucose (mg/dL)	89.0 (83.0, 98.0)	89.0 (83.0, 98.0)	88.0 (82.0, 98.0)	0.3
Serum insulin (μmol/L)	5.3 (3.5, 8.4)	5.3 (3.5, 8.3)	5.3 (3.5, 8.4)	0.9
Hemoglobin A _{1c} (%)	5.5 (5.2, 5.8)	5.5 (5.2, 5.8)	5.5 (5.2, 5.8)	0.1
Total cholesterol (mg/dL)	193.0 (170.0, 216.0)	192.0 (171.0, 213.0)	192.5 (171.0, 216.0)	0.7
HDL cholesterol (mg/dL)	49.0 (40.0, 59.0)	48.0 (40.0, 60.0)	48.0 (41.0, 58.0)	0.6
LDL cholesterol (mg/dL)	117.0 (96.0, 138.0)	115.0 (96.0, 134.0)	118.0 (96.5, 137.0)	0.4
Triglycerides (mg/dL)	108.0 (77.0, 155.0)	111.0 (77.0, 160.0)	111.0 (77.0, 163.0)	0.4
C-Reactive protein (mg/L)	1.76 (0.80, 3.94)	1.79 (0.77, 4.05)	1.93 (0.81, 4.38)	0.10
Urinary albumin (mg/dL)	0.60 (0.30, 1.3)	0.60 (0.30, 1.0)	0.60 (0.30, 1.1)	<0.001
Urinary creatinine	108.6 (60.6, 165.2)	110.7 (60.1, 165.1)	110.7 (61.2, 166.1)	0.7
Urinary albumin-creatinine ratio (mg/g)	5.51 (3.40, 10.80)	4.80 (3.09, 8.60)	5.00 (3.20, 9.40)	<0.001

Note: N = 4,594. Categorical variables are given as number (percentage); continuous variables are shown as median (25th, 75th percentile). Conversion factors for units: cholesterol in mg/dL to mmol/L, $\times 0.02586$; triglycerides in mg/dL to mmol/L, $\times 0.05551$.

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; CRAE, central retinal artery equivalent; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent task.

^aTotal intentional exercise (Q9-15).

^bIn those with hypertension.

Table 3

Baseline Characteristics of Participants Stratified by Retinal Venular Caliber Tertiles

	CRVE			<i>P</i>
	Lowest Tertile	Middle Tertile	Highest Tertile	
Men	676 (45.8)	763 (49.5)	753 (47.8)	0.1
Race				<0.001
White	825 (55.9)	596 (38.7)	409 (26.0)	
Chinese American	158 (10.7)	185 (12.0)	189 (12.0)	
African American	228 (15.4)	400 (25.9)	610 (38.7)	
Hispanic	266 (18.0)	361 (23.4)	367 (23.3)	
Hypertension	601 (40.7)	570 (37.0)	655 (41.6)	<0.001
Antihypertensive treatment ^a	438 (72.9)	412 (72.3)	502 (76.6)	0.2
ACE-inhibitor use	146 (9.9)	138 (9.0)	193 (12.3)	0.007
Lipid-lowering medication	218 (14.8)	214 (13.9)	237 (15.1)	0.6
Family history of diabetes	201 (13.7)	218 (14.2)	235 (15.0)	0.2
Smoking status				<0.001
Nonsmoker	801 (54.4)	782 (50.9)	682 (43.7)	
Ex-smoker	578 (39.3)	590 (38.4)	599 (38.4)	
Current	93 (6.3)	164 (10.7)	281 (18.0)	
Age (y)	61 (53, 69)	59 (52, 67)	58 (51, 66)	<0.001
Systolic blood pressure (mm Hg)	122.0 (110.0, 137.0)	120.5 (109.0, 135.5)	121.5 (109.5, 138.0)	<0.001
Diastolic blood pressure (mm Hg)	71.0 (64.5, 78.0)	72.0 (65.0, 78.5)	72.0 (65.5, 79.0)	<0.001
BMI (kg/m ²)	30.0 (24.1, 30.4)	27.6 (24.6, 30.9)	28.5 (25.1, 32.1)	<0.001
Physical activity (MET-min/wk) ^b	945.0 (300.0, 2,212.5)	915.0 (210.0, 2,100.0)	787.5 (52.5, 1,920.0)	<0.001
Fasting plasma glucose (mg/dL)	88.0 (82.0, 96.0)	89.0 (83.0, 97.0)	90.0 (83, 101.0)	<0.001
Serum insulin (μmol/L)	4.8 (3.2, 7.5)	5.4 (3.5, 8.4)	5.9 (3.9, 9.2)	<0.001
Hemoglobin A _{1c} (%)	5.4 (5.1, 5.7)	5.5 (5.2, 5.8)	5.6 (5.3, 6.0)	<0.001
Total cholesterol (mg/dL)	193.0 (171.0, 216.0)	193.0 (171.0, 216.0)	192.0 (170.0, 214.0)	0.4
HDL cholesterol (mg/dL)	51.0 (42.0, 63.0)	48.0 (40.0, 58.0)	47.0 (39.0, 56.0)	<0.001
LDL cholesterol (mg/dL)	115.0 (95.0, 135.0)	118.0 (98.0, 136.0)	117.0 (96.0, 137.0)	0.05
Triglycerides (mg/dL)	105.0 (73.0, 152.0)	109.0 (77.0, 160.0)	115.0 (82.0, 166.0)	<0.001
C-Reactive protein (mg/L)	1.53 (0.69, 3.67)	1.67 (0.75, 3.92)	2.17 (0.97, 4.69)	<0.001
Urinary albumin (mg/dl)	0.50 (0.30, 1.10)	0.55 (0.30, 1.10)	0.60 (0.30, 1.10)	<0.001
Urinary creatinine	102.8 (54.0, 156.9)	105.9 (60.8, 164.1)	110.6 (61.2, 166.1)	<0.001
Urinary albumin-creatinine ratio (mg/g)	5.0 (3.2, 9.7)	4.9 (3.1, 8.6)	5.1 (3.2, 9.9)	0.3

Note: N = 4,594. Categorical variables are given as number (percentage); continuous variables are shown as median (25th, 75th percentile). Conversion factors for units: cholesterol in mg/dL to mmol/L, x0.02586; triglycerides in mg/dL to mmol/L, glucose in mg/dL to mmol/L, x0.05551.

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; CRVE, central retinal venular equivalent; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent task.

^aIn those with hypertension.

^bTotal intentional exercise (Q9-15).

Table 4
Cox Proportional Hazard Model of the Association Between Retinal Vascular Caliber and Incident CKD3

	Person-Time (y)	Incident CKD3 Cases (no.)	Incident CKD3 Rate ^a	Model 1		Model 2		Model 3	
				HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Retinal arteriolar caliber									
Tertile 3, ≥150 μm	7,297	68	9.3 (7.3-11.8) ^b	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Tertile 2, 139-150 μm	7,096	66	9.3 (7.3-11.8) ^b	0.87 (0.61-1.24)	0.5	1.20 (0.84-1.70)	0.33	1.11 (0.89-1.60)	0.6
Tertile 1, ≤139 μm	6,706	98	14.6 (12.0-17.8) ^b	1.20 (0.85-1.69)	0.3	0.84 (0.58-1.21)	0.35	0.82 (0.57-1.18)	0.3
Retinal venular caliber									
Tertile 1, ≤205 μm	6,728	90	13.3 (11.1-16.4) ^c	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Tertile 2, 205-223 μm	7,095	78	11.1 (8.8-13.7) ^c	1.13 (0.81-1.56)	0.5	1.15 (0.83-1.59)	0.39	1.14 (0.83-1.59)	0.4
Tertile 3, ≥223 μm	7,276	64	8.7 (6.8-11.2) ^c	0.99 (0.69-1.42)	0.9	0.96 (0.66-1.38)	0.82	0.94 (0.65-1.36)	0.8

Note: Model 1 adjusted for age, sex, study center, and venular caliber (in models of arteriolar caliber) or arteriolar caliber (in models of venular caliber), stratified by ethnicity; model 2 adjusted for variables in model 1 plus systolic blood pressure, medication for diabetes, diabetes status, antihypertensive medications, body mass index, triglyceride level, smoking status, fasting glucose level, C-reactive protein level, and hemoglobin A_{1c} level, stratified by ethnicity; and model 3 adjusted for variables in model 2 plus logACR and presence of any retinopathy, stratified by ethnicity.

Abbreviations: ACR, albumin-creatinine ratio; CI, confidence interval; CKD3, CKD stage 3; HR, hazard ratio.

^a Per 1,000 person-years.

^b *P* for trend < 0.001.

^c *P* for trend = 0.03.

Table 5
Cox Proportional Hazard Model of the Association Between Retinal Vascular Caliber and Incident CKD Stage 3 by Ethnicity

	White (n = 1,830)			Chinese-American (n = 532)			African American (n = 1,238)			Hispanic (n = 994)		
	HR	(95% CI)	P	HR	(95% CI)	P	HR	(95% CI)	P	HR	(95% CI)	P
Retinal arteriolar caliber												
Tertile 3, ≥150 μm	1.00	(reference)		1.00	(reference)					1.00	(reference)	
Tertile 2, 139-150 μm	1.67	(0.95-2.94)	0.07	0.82	(0.18-3.75)	0.8	0.49	(0.24-0.98)	0.05	0.32	(0.11-1.00)	0.05
Tertile 1, ≤139 μm	1.78	(1.01-3.15)	0.04	0.65	(0.23-1.79)	0.4	0.81	(0.39-1.68)	0.6	0.86	(0.37-2.02)	0.7
Retinal venular caliber												
Tertile 1, ≤205 μm	1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)	
Tertile 2, 205-223 μm	1.22	(0.81-1.84)	0.3	1.97	(0.56-7.00)	0.7	1.63	(0.71-3.73)	0.3	0.66	(0.30-1.47)	0.3
Tertile 3, ≥223 μm	0.89	(0.50-1.57)	0.7	1.78	(0.31-10.19)	0.3	1.14	(0.50-2.63)	0.7	0.45	(0.17-1.22)	0.1

Note: Adjusted for variables in model 1 plus systolic blood pressure, diabetes status, medication for diabetes, antihypertensive medications, body mass index, triglyceride level, smoking status, fasting glucose level, C-reactive protein level, hemoglobin A_{1c} level, logACR, and any retinopathy.

Abbreviations: ACR, albumin-creatinine ratio; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.

Cox Proportional Hazard Model of the Association Between Retinal Vascular Caliber and Incident CKD Stage 3 in Whites Without DM and Without HTN

Table 6

	People w/o DM (n = 1,526)			People w/o HTN (n = 1,205)			People w/o HTN and DM		
	HR (95% CI)	P		HR (95% CI)	P		HR (95% CI)	P	
Retinal arteriolar caliber									
Tertile 3, ≥150 μm	1.00 (reference)			1.00 (reference)			1.00 (reference)		
Tertile 2, 139-150 μm	1.60 (0.84-3.04)	0.2		2.32 (0.99-5.47)	0.05		2.90 (1.05-9.94)	0.04	
Tertile 1, ≤139 μm	1.72 (0.90-3.32)	0.09		2.96 (1.24-7.06)	0.01		2.95 (1.10-7.98)	0.03	
Retinal venular caliber									
Tertile 1, ≤205 μm	1.00 (reference)			1.00 (reference)			1.00 (reference)		
Tertile 2, 205-223 μm	1.01 (0.63-1.62)	0.9		1.05 (0.56-2.02)	0.9		0.79 (0.38-1.65)	0.5	
Tertile 3, ≥223 μm	0.82 (0.44-1.52)	0.5		0.74 (0.30-1.84)	0.5		0.61 (0.23-1.65)	0.3	

Note: Adjusted for variables in model 1 plus systolic blood pressure, medication for diabetes, diabetes status, antihypertensive medications, body mass index, triglyceride level, smoking status, fasting glucose level, C-reactive protein level, hemoglobin A_{1c} level, logACR, and any retinopathy.

Abbreviations: ACR, albumin-creatinine ratio; CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension.