Retinopathy and Cognitive Impairment in Adults With CKD

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Abstract

Background—Retinal microvascular abnormalities have been associated with cognitive impairment, possibly serving as a marker of cerebral small vessel disease. This relationship has not been evaluated among persons with chronic kidney disease (CKD), a condition associated with increased risk of both retinal pathology and cognitive impairment.

Study Design—Cross-sectional study

Setting & Participants—588 participants   52 years old with CKD in the Chronic Renal Insufficiency Cohort (CRIC) Study

Predictor—Retinopathy graded using the Early Treatment Diabetic Retinopathy Study severity scale and diameters of retinal vessels.

Outcomes—Neuropsychological battery of six cognitive tests

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[*]N SECTION: A list of the Chronic Renal Insufficiency Cohort (CRIC) Study group has been previously published.[1]

Measurements—Logistic regression models were used to evaluate the association of retinopathy, individual retinopathy features, and retinal vessel diameters with cognitive impairment (1 SD from the mean), and linear regression models were used to compare cognitive test scores across levels of retinopathy adjusting for age, race, sex, education, and medical comorbidities.

Results—The mean age of the cohort was 65.3 +/− 5.6 (SD) years; 51.9% were non-White, and 52.6% were male. The prevalence of retinopathy was 30.1% and 14.3% for cognitive impairment. Compared to those without retinopathy, participants with retinopathy had increased likelihood of cognitive impairment on executive function (35.1% vs. 11.5%; OR, 3.4; 95% CI, 2.0-6.0), attention (26.7% vs. 7.3%; OR, 3.0; 95% CI, 1.8-4.9), and naming (26.0% vs. 10.0%; OR, 2.1; 95% CI, 1.2-3.4) after multivariable adjustment. Increased level of retinopathy was also associated with lower cognitive performance on executive function and attention. Microaneurysms were associated with cognitive impairment on some domains, but there were no significant associations with other retinal measures after multivariable adjustment.

Limitations—Unknown temporal relationship between retinopathy and impairment.

Conclusions—In adults with CKD, retinopathy is associated with poor performance on several cognitive domains including executive function and attention. Evaluation of retinal microvascular abnormalities may be a promising tool for identifying patients with CKD who are at increased risk of cognitive impairment.

Cerebrovascular disease (CVD) is associated with an increased risk of cognitive impairment, but traditional methods of assessing CVD are both expensive and invasive. Alternatively, evaluation of fundus photography to identify retinal microvascular abnormalities such as retinopathy could be used to evaluate markers of CVD and target those at risk for cognitive impairment.[1] Several cross-sectional studies have reported that participants with retinopathy performed worse on cognitive tests[2-5] and had an increased risk of cognitive decline.[6] This relationship between retinal microvascular abnormalities and cognitive impairment is especially significant for populations at high risk for cognitive impairment.[7-9] For example, among participants with type I or type II diabetes, retinopathy has been reported to be associated with cognitive impairment,[8, 10] and among participants with hypertension, it has been shown that those with retinopathy may be two times more likely to have dementia or cognitive impairment.[2, 4]

Individuals with chronic kidney disease (CKD) are also at high risk for cognitive impairment,[11-13] and, despite reports that retinopathy is also associated with a greater risk of decreased kidneyfunction,[14, 15] to our knowledge no studies have examined the association between retinopathy and cognitive impairment in this high risk population. A recent study found that diabetic participants with cognitive decline were more likely to have both retinopathy and nephropathy,[16] indicating that cognitive impairment, decreased kidneyfunction, and retinopathy could share similar metabolic and inflammatory pathways.[17, 18] The aim of our study is to investigate the association between retinopathy and cognitive function in a cohort of patients with chronic kidney disease.

Methods

Study Population

Between May 2003 and March 2007, participants were enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study, which included 3,612 adults with chronic kidney disease (CKD) and was designed to investigate the epidemiology of CKD and its relationship to cardiovascular disease. The study design and methods as well as the baseline cohort characteristics have been described elsewhere.[19, 20] Two of the ancillary studies of the CRIC study are RCRIC (Retinopathy in Chronic Renal Insufficiency Cohort)[21] and CRIC COG (Cognitive Function in Chronic Renal Insufficiency Cohort).[22] In RCRIC, digital photos of the disc and macula in both eyes of 1936 of the 2605 (74%) participants in the CRIC Study from 6 of the 7 recruitment sites (Ann Arbor, Michigan; Baltimore, Maryland; Chicago, Illinois; Cleveland, Ohio; Philadelphia, Pennsylvania; and Oakland, California) were collected and evaluated. In CRIC COG, cognitive function measures from 825 participants (83.9 % of those asked participated,; eligibility criteria, age 52 years) from 4 of the study sites (Chicago, Cleveland, Philadelphia, and Oakland) were annually collected. Of the 638 participants enrolled in both ancillary studies, whether retinopathy was present could be determined in 588, and central retinal artery and vein diameters were measured in 512. We were able to assess individual features of retinopathy in at least 538 participants (microaneurysms, 538; hemorrhages, 546; soft exudates, 546; and hard exudates, 551). Compared to participants enrolled in both ancillary studies, other CRIC participants had slightly lower education levels, higher BMI, lower eGFR, and lower 3MS score (p<0.05).

Fundus Pathology and Retinopathy

Between June 2006 and May 2008, fundus photography was completed for both eyes by trained staff, and photographs were evaluated for fundus pathology and vascular abnormalities by blinded trained graders at a centralized site, the Fundus Photograph Reading Center at the University of Pennsylvania.[23] The primary retinal measure used in these analyses was the overall retinopathy score, which was graded according to the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale, a grading protocol previously used in nondiabetic populations.[24, 25] Presence of retinopathy was defined as an ETDRS score of 14, 15, 20, 35, 43, 47, 53, 60, 65, 70, or 80. We also grouped the retinopathy scores into four categories: no retinopathy (ETDRS score: 10 or 12), mild non-proliferative retinopathy (ETDRS score: 14, 15, or 20), non-proliferative retinopathy (ETDRS score: 35, 43, 47, or 53), and proliferative retinopathy (ETDRS score: 60, 65, 70, or 80). Presence/absence of each of the individual components of the ETDRS score, microaneurysms, hemorrhages, and hard and soft exudates, was also evaluated. Each of these measures was done for both eyes of each participant when possible. For CRIC participants with eye examinations, both eyes were measured 90.0% of the time for retinopathy scores, 80.2% for central retinal artery and vein diameters, 72.2% for microaneurysms, 73.3% for retinal hemorrhages, 74.1% for hard exudates, and 73.5% for soft exudates. For retinopathy features, when measures were made on both eyes, we chose the higher of the two scores. Retinal artery and vein diameters were also measured using the ARIC protocol and IVAN software (University of Wisconsin;the 6 largest retinal arteries

and 6 largest retinal veins were measured to determine the mean diameters for arteries and for veins),[26, 27] and we used the mean of the two eyes. For all of these measures, if only one eye was evaluated, the score for that eye was used. Further details on methods of retinal photography can be found elsewhere.[21, 23]

Cognitive Measures

The CRIC COG study included a battery of 6 interviewer-administered cognitive function tests: Modified Mini-Mental State Examination (3MS) to assess global cognitive function;[28] Trail-Making Test, Forms A and B (Trails A and B), which are tests of attention and executive function;[29] Category (verbal) Fluency, which measures verbal production, semantic memory, and language; Buschke Selective Reminding Test, which assesses delayed memory;[30] and the Boston Naming Test, which measures language function based on naming pictures of objects.[31] For each participant, we used the CRIC COG information collected nearest to the date of the RCRIC photographs (between July 2006 and October 2008). These measures were collected on the same day for 81% of participants and within 6 months for 96% of participants, and all were within 14 months of each other (median, 0 [range, 0-409] days). For all measures except the Trails A and B, a higher score indicated better cognitive function. Cognitive impairment was defined as a test score which was more than 1 standard deviation (SD) smaller than the mean for 3MS, Category Fluency, Boston Naming, and Buschke, and a score larger than 1 SD greater than the mean for Trails A and B.

Covariates

Sociodemographic risk factors such as age, sex, race, education, smoking, and self-reported medical history (including diagnosed hypertension and diabetes and self-reported coronary artery disease and stroke) were evaluated as part of the CRIC study visit, which coincided with the CRIC-COG cognitive evaluation. Body mass index (BMI) was calculated from measured weight and height, and estimated glomerular filtration rate (eGFR) was determined using the IDMS-traceable 4-variable Modification of Diet in Renal Disease (MDRD) Study equation.[32,32a] Blood pressure was measured using a standardized protocol.[33] High sensitivity C-reactive protein was assayed using a BN II nephelometer (Siemens), urine albumin was measured with spot urine samples using an Immulite system (Siemens), and proteinuria was measured by 24 hour urine collection. Each covariate had <5% missing data, except for proteinuria which had 12% missing data.

Statistical analysis

Demographic and clinical measures were compared between those with and without retinopathy, and those with and without cognitive impairment, using two-sample t-tests for normally distributed continuous variables (using the Satterthwaite adjustment when variances are not equal), Wilcoxon rank sum tests for non-Normally distributed continuous variables, and chi-squared tests for categorical variables. To study the relationship between the cognitive measures and level of retinopathy, we first computed the mean and SD of each cognitive measure for each level of retinopathy. The means of the cognitive measures were compared across level of the retinal pathology using either an analysis of variance (ANOVA) for the 4-level retinopathy category (no, mild non-proliferative, non-proliferative,

and proliferative retinopathy), or two-sample t-tests for dichotomous retinopathy designation (yes, no). For the ANOVA models using the 4-level retinopathy variable, we tested for trend using orthogonal polynomial contrasts. Finally, to adjust for possible confounders, we fitted linear regression models with cognitive test score as the dependent variable, and the following independent variables: presence or absence of retinal pathology, age, race, and education. We used logistic regression to calculate the odds of cognitive impairment associated with retinal pathology, adjusting for age, race, and education. In additional models, we adjusted for medical comorbidities including coronary artery disease, hypertension, diabetes, and stroke. SAS v9.1 (SAS Institute Inc) was used for all analyses. Statistical testing was two-tailed with significance level set at 0.05.

Results

The mean age of participants whose retinopathy status could be determined was 65.3 +/− 5.6 (SD) years; 51.9% of the cohort were non-White, and 52.6% were male. Thirty percent of participants showed evidence of retinopathy: 7.7% with mild non-proliferative, 12.9% with non-proliferative, and 9.5% with proliferative retinopathy. Participants with retinopathy were younger; less likely to have completed high school; less likely to be White; and more likely to have higher systolic blood pressure, diabetes, urinary protein coronary artery disease, and a history of stroke (p<0.05 for all). In addition, mean eGFR was lower for those with retinopathy (p<0.001) (Table 1). Compared to those without cognitive impairment, participants with cognitive impairment were older; less likely to be White; less likely to have completed high school; more likely to have a history of stroke; and more likely to have higher systolic blood pressure, higher urinary protein, lower BMI, and lower eGFR (p<0.05) (Table 2).

Participants with retinopathy were more likely to have cognitive impairment than those without retinopathy. In unadjusted logistic regression models of cognitive impairment, retinopathy was significantly associated with impairment on all cognitive measures except for Buschke Selective Reminding (3MS: OR, 1.7; 95% CI, 1.1-2.8; Trails A: OR, 4.6; 95% CI, 2.8-7.6; Trails B: OR, 4.2; 95% CI, 2.7-6.4; Category Fluency: OR, 2.1; 95% CI, 1.3-3.2; Boston Naming Test: OR, 3.2; 95% CI, 2.0-5.0; Buschke Selective Reminding: OR, 1.4; 95% CI, 0.9-2.2) (Figure 1). After multivariable adjustment for age, race, sex, and education, retinopathy remained associated with risk of cognitive impairment on Trails A (OR,3.4; 95% CI, 2.0-6.0), Trails B (OR,3.0; 95% CI, 1.8-4.9), and the Boston Naming Test (OR, 2.1; 95% CI, 1.2-3.4).

Performance on cognitive tests was worse as severity of retinopathy increased. For example, on Trails A, there was a trend towards worse performance with increasing severity of retinopathy (no retinopathy, mean of 45.2 +/− 1.5 [SE]; mild non-proliferative retinopathy, 52.9 +/− 4.5; non-proliferative retinopathy, 64.7 +/− 3.4; and proliferative retinopathy, 82.7 +/− 4.0; p for trend <0.001) (Table 3). Unadjusted scores on the 3MS, Trails B, Category Fluency, Buschke Selective Reminding, and Boston Naming tests also had significant trends across levels of retinopathy (Table 3). After multivariable adjustment for age, race, sex, and education, the relationship between increased severity of retinopathy and worse performance on Trails A and Trails B remained statistically significant.

We next determined whether individual retinal microvascular abnormalities were associated with cognitive function among patients with CKD. In models of cognitive impairment adjusted for age, race, sex, and education (Figure 2), microaneurysms were significantly associated with impairment on Trails B and Category Fluency (ORs of 2.8 [95% CI, 1.2-6.4] and 2.9 [95% CI, 1.4-6.4], respectively). Mean cognitive scores on Trails A and B were also significantly worse for those with microaneurysms compared to those without (Table 4). None of the cognitive impairment measures were significant for hemorrhages or hard exudates, and there were too few participants with soft exudates (n=14) to determine their association with cognitive impairment.

In order to determine whether the association between retinopathy and cognitive impairment was mediated by cardiovascular disease, diabetes, or albumin (as a proxy for small vessel disease), we also adjusted for additional variables including systolic blood pressure, coronary artery disease, stroke, BMI, diabetes, or albumin. The addition of each of the variables did not attenuate the association between cognitive impairment and retinopathy. To determine the effects of kidney function, we stratified models by eGFR level. The pattern of the association between retinopathy and cognitive performance was similar but tended to be more robust for eGFR>30 mL/min/1.73 m^2 on Trails A, Trails B, and Boston Naming. In models stratified for diabetes status, retinopathy was more consistently associated with cognitive performance for those without diabetes.

Analyses testing for trend in unadjusted mean test scores across quartiles of central artery and central vein diameter were not significant for most cognitive measures. Unadjusted scores on Trails A had significant trends across quartiles of central vein diameter, but after adjusting for age, race, sex, and education, the association was no longer significant. Central vein diameter was associated with impairment on the 3MS and Boston Naming Test in unadjusted models, but was not significant for any of the adjusted models.

Discussion

In this cohort of persons with chronic kidney disease, retinopathy was significantly associated with cognitive impairment. In particular, the odds of cognitive impairment on executive function, attention, and naming were two to three times higher in those with retinopathy compared to those without retinopathy, but there was no association for global cognition, category fluency, or delayed recall. Significant associations between retinopathy and cognitive impairment on executive function, attention, and naming persisted after adjusting for diabetes and cardiovascular disease. Similar relationships were observed for specific retinal microvascular abnormalities including microaneurysms, while central vein and central artery diameter, hemorrhages, and soft and hard exudates were not associated with cognitive function.

Impairment on executive function, as linked to retinopathy in this study, is associated with the frontal subcortical region of the brain, an area which is particularly vulnerable to damage from cerebral small vessel disease.[34] Our findings are supported by previous reports on the relationship between retinopathy and cognitive impairment in both general populations as well as among patients with hypertension and diabetes. In the Cardiovascular Health Study,

retinopathy was associated with impairment on the Digit Symbol Substitution Test, a test of executive function, but not on the Modified Mini-Mental State Examination.[2] In the Atherosclerosis Risk in the Community (ARIC) cohort, the presence of retinopathy increased the risk of cognitive decline on tests of executive function and psychomotor speed, and the likelihood of cognitive impairment was almost three times higher for those with microaneurysms or hemorrhages.[5, 6] Measures of central retinal artery and central retinal venular diameter were not significant in our study. While both venular dilation and arteriolar narrowing have been associated with risk of cognitive impairment and dementia in previous studies,[4, 35] the evidence of a relationship between these measures of retinal microvascular abnormalities and cognitive impairment is not as consistent as with retinopathy. Similarly, retinopathy has also been associated with decreased kidneyfunction,[14, 15, 36] but associations of CKD with central vein and central artery diameter have been mixed.[36-38] It is possible that in retinopathy, microaneurysms may reflect more severe microvascular damage than arteriolar narrowing or venular dilation.[39]

Our findings support the hypothesis that CKD, retinopathy, and cognitive impairment share common vascular pathways. These mechanisms could include endothelial dysfunction, inflammation, oxidative stress, and vascular calcification,[18, 40] suggesting that a systemic approach to small vessel disease which links outcomes in multiple organs may be appropriate.[17] This perspective would be especially critical for patients with chronic kidney disease, a population at increased risk for cognitive impairment.[13, 22, 41] Moreover, in dialysis patients, cognitive impairment and dementia have also been linked to increased risk of other adverse health outcomes including dialysis withdrawal and death.[42-44] Although several studies have demonstrated a link between CKD and cognitive impairment, little is known about effective strategies to prevent cognitive decline in this population. As such, our study, which demonstrates a relationship between retinopathy and cognitive impairment independent of coronary artery disease, hypertension, diabetes, and stroke, has possible implications for monitoring patients with CKD and suggests that fundus pathology would be a useful noninvasive and inexpensive marker for identifying those at risk of cognitive impairment. This is supported by a recent study which demonstrated an association between retinopathy and markers of cerebral small vessel disease, including cerebral and lacunar infarcts identified by magnetic resonance imaging 10 years later.[45]

To our knowledge, this is the first study to examine the relationship between retinopathy and cognitive impairment in patients with CKD. Unlike previous investigations of retinal microvascular abnormalities and cognition, we administered an extensive battery of six cognitive tests in the CRIC Study to assess impairment on multiple cognitive domains. However, because we report on cross sectional findings, the temporal relationship between retinopathy and cognitive impairment is unclear. In addition, although protocols for retinal photography and grading were standardized, there may be some variation between graders.

In our cohort of adults with CKD, retinopathy was significantly associated with cognitive impairment on several domains including executive function, attention and naming. Our initial findings indicate that cerebral small vessel disease may play a role in the association between CKD and development of cognitive impairment. The prevalence of CKD is expected to rise in the U.S. as the population ages and the incidence of cardiovascular risk

factors such as obesity also increases.[46] Thus, approaches are needed to target persons with CKD who are at increased risk for cognitive decline and dementia if the public health burden of these diseases is to be reduced. Identification of retinal pathology by fundus photography as a proxy for cerebral small vessel disease is a promising approach, but longitudinal studies are needed to establish the temporal relationship between retinopathy and changes in cognitive function in the setting of CKD.

Acknowledgments

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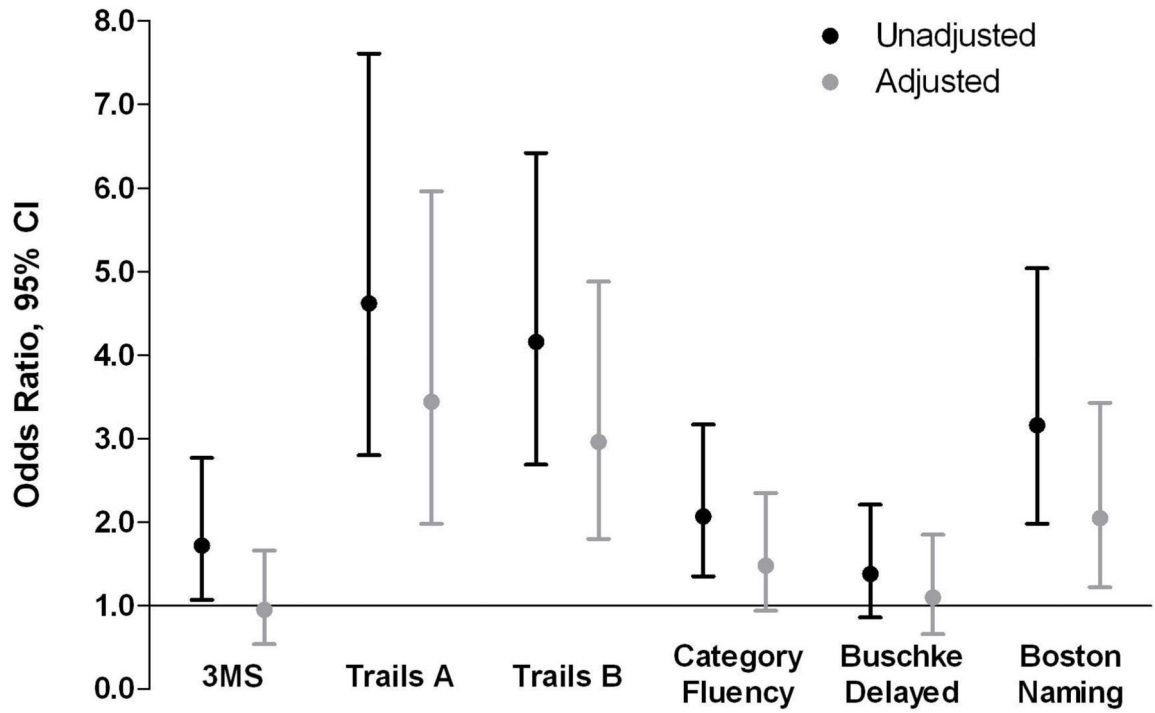
Figure 1.
Unadjusted and adjusted (for age, race, sex, and education) odds of cognitive impairment for those with versus without retinopathy
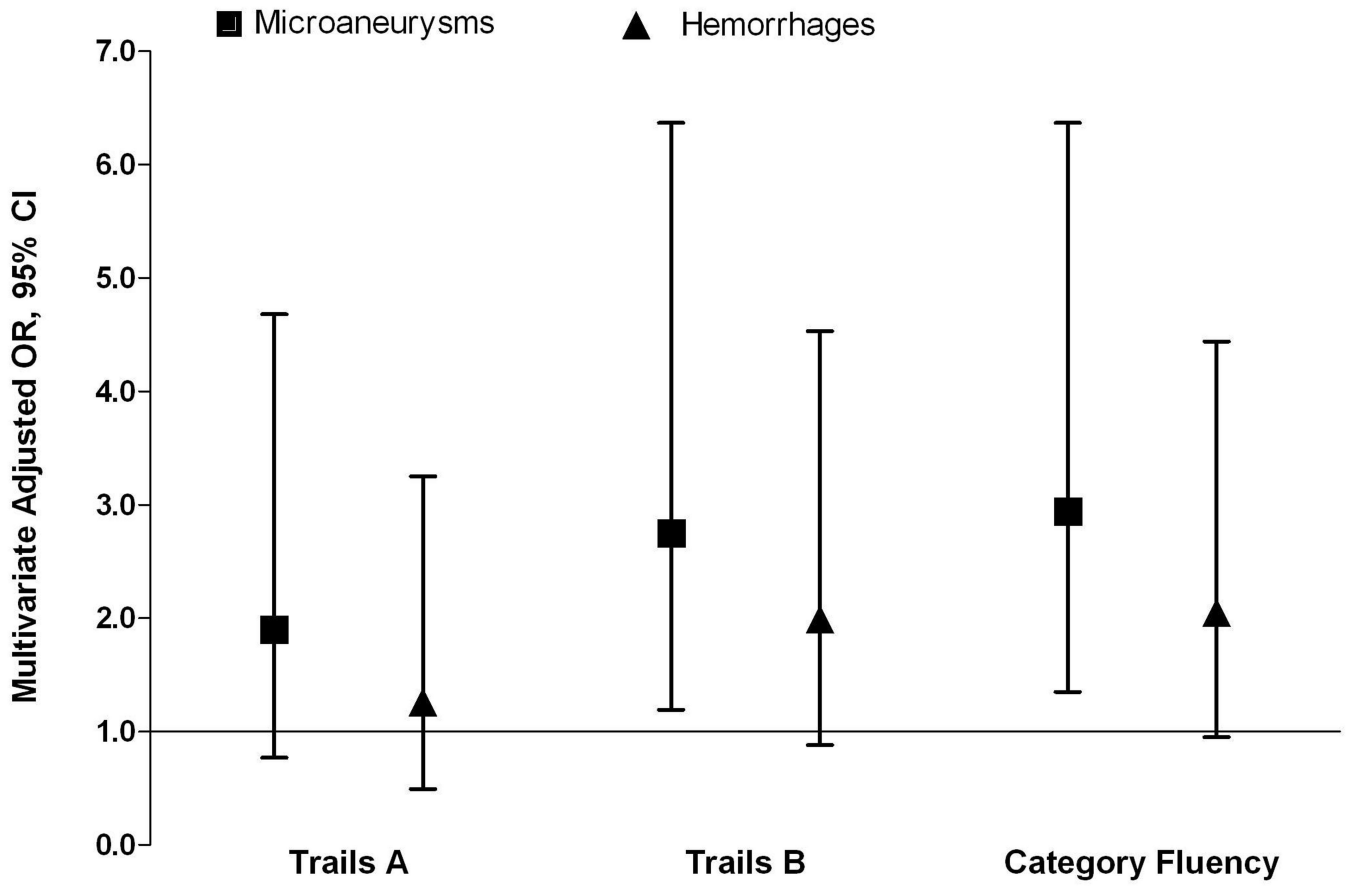
Figure 2.
Odds of cognitive impairment in those with versus without microaneurysms or with versus without hemorrhages, adjusted for age, race, sex and education

Table 1

Baseline characteristics of CRIC Study participants by retinopathy status

Baseline characteristics	Total N=588	No Retinopathy n=411	Retinopathy n=177	p-value[a]
Age (y)	65.3 (5.6)	65.6 (5.4)	64.5 (6.0)	0.03
Male sex	309 (52.6)	209 (50.9)	100 (56.5)	0.2
White	283 (48.1)	235 (57.2)	48 (27.1)	<0.001
High School education	500 (85.0)	366 (89.1)	134 (75.7)	<0.001
Systolic BP (mmHg)	128.8 (22.1)	125.7 (20.2)	136.0 (24.6)	<0.001
Diastolic BP(mmHg)	68.0 (12.1)	67.6 (11.2)	69.0 (14.1)	0.2
Diabetes	275 (46.8)	133 (32.4)	142 (80.2)	<0.001
Coronary Artery Disease	168 (28.6)	105 (25.6)	63 (35.6)	0.01
Stroke	76 (12.9)	43 (10.5)	33 (18.6)	0.007
BMI (kg/m^2)	31.2 (6.7)	31.0 (6.7)	31.9 (6.6)	0.1
Ever Smoker	347 (59.0)	246 (59.9)	101 (57.1)	0.5
eGFR category[b]				<0.001
0-29 mL/min/1.73m^2	120 (21.0)	59 (14.6)	61 (36.1)	
30-44 mL/min/1.73m^2	202 (35.3)	139 (34.5)	63 (37.3)	
45-59 mL/min/1.73m^2	200 (35.0)	161 (40.0)	39 (23.1)	
60 mL/min/1.73m^2	50 (8.7)	44 (10.9)	6 (3.6)	
Albumin (g/dL)	3.98 (0.40)	4.04 (0.39)	3.84 (0.40)	<0.001
Proteinuria (g/24 h)	0.13 (0.05, 0.42)	0.10 (0.05, 0.24)	0.32 (0.09, 1.17)	<0.001
C-reactive protein (mg/dL)	2.17 (0.97, 5.83)	2.15 (0.97, 5.69)	2.22 (0.95, 6.25)	0.6
Cognitive Impairment[c]				
3MS	84 (14.3)	50 (12.2)	34 (19.2)	0.03
Trails A	77 (13.1)	30 (7.3)	47 (26.7)	<0.001
Trails B	108 (18.5)	47 (11.5)	61 (35.1)	<0.001
Category Fluency	111 (18.9)	63 (15.4)	48 (27.3)	<0.001
Buschke Selective Reminding	91 (15.7)	58 (14.3)	33 (18.8)	0.2

Baseline characteristics	Total N=588	No Retinopathy n=411	Retinopathy n=177	p-value[a]
Boston Naming	87 (14.8)	41 (10.0)	46 (26.0)	<0.001

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean +/− SD or median [interquartile range].

CRIC, Chronic Renal Insufficiency Cohort; BP, blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate;3MS, Modified Mini-Mental State Examination; SD, standard deviation.

[a] p-value for comparison of no retinopathy and retinopathy groups

[b] n=572

[c] Cognitive impairment defined by the listed neuropsychological tests, as values more than 1 SD above the mean for Trails A and B, and more than 1 SD below the mean for the other tests

Table 2

Baseline characteristics of CRIC Study participants by cognitive impairment status

Baseline characteristics	Total N=588	No Cognitive Impairment n=504	Cognitive Impairment n=84	p-value[b]
Age (y)	65.3 (5.6)	65.0 (5.6)	66.8 (5.7)	0.005
Male sex	309 (52.6)	267 (53.0)	42 (50.0)	0.6
White	283 (48.1)	268 (53.2)	15 (17.9)	<0.001
High School education	500 (85.0)	460 (91.3)	40 (47.6)	<0.001
Systolic BP (mmHg)	128.8 (22.1)	126.8 (20.6)	140.5 (26.9)	<0.001
Diastolic BP (mmHg)	68.0 (12.1)	67.7 (11.8)	69.9 (13.9)	0.2
Diabetes	275 (46.8)	229 (45.4)	46 (54.8)	0.1
Coronary Artery Disease	168 (28.6)	143 (28.4)	25 (29.8)	0.8
Stroke	76 (12.9)	52 (10.3)	24 (28.6)	<0.001
BMI(kg/m^2)	31.2 (6.7)	31.5 (6.9)	29.8 (4.8)	0.008
Ever Smoker	347 (59.0)	296 (58.7)	51 (60.7)	0.7
eGFR[c] category				0.002
0-29 mL/min /1.73m^2	120 (21.0)	93 (18.9)	27 (33.8)	
30-44 mL/min /1.73m^2	202 (35.3)	170 (34.6)	32 (40.0)	
45-59 mL/min /1.73m^2	200 (35.0)	181 (36.8)	19 (23.8)	
60 mL/min/1.73m^2	50 (8.7)	48 (9.8)	2 (2.5)	
Albumin(g/dL)	3.98 (0.40)	3.98 (0.40)	3.99 (0.44)	0.8
C-reactive protein (mg/dL)	2.17 (0.97, 5.83)	2.03 (0.92, 5.71)	2.76 (1.25, 6.25)	0.09
Proteinuria (g/24 h)	0.13 (0.05, 0.42)	0.12 (0.05, 0.38)	0.22 (0.08, 0.63)	0.04

Note: Cognitive impairment defined as values more than 1 SD below the mean on the Modified Mini-Mental State Examination. Values for categorical variables are given as number (percentage); values for continuous variables are given as mean +/− SD or median [interquartile range].

CRIC, Chronic Renal Insufficiency Cohort; BP, blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate;SD, standard deviation.

[b] p-value for comparison of no cognitive impairment and cognitive impairment groups

[c] n=572

Table 3

Cognitive test scores by level of retinopathy

	None (n=411)	Mild Non-Proliferative (n=45)	Non-Proliferative (n=76)	Proliferative (n=56)	p-value[a]
3MS					
Unadjusted	94.1 (0.4)	92.5 (1.1)	91.9 (0.8)	90.8 (1.0)	0.002
Adjusted[b]	91.0 (0.4)	91.1 (1.0)	91.1 (0.8)	90.8 (0.9)	0.9
Trails A					
Unadjusted	45.2 (1.5)	52.9 (4.5)	64.7 (3.4)	82.7 (4.0)	<0.001
Adjusted[b]	53.0 (2.0)	56.7 (4.4)	65.5 (3.5)	84.1 (4.1)	<0.001
Trails B					
Unadjusted	122.1 (3.7)	152.8 (11.0)	171.5 (8.6)	192.7 (10.0)	<0.001
Adjusted[b]	150.0 (4.5)	168.9 (10.0)	174.8 (8.1)	195.8 (9.3)	0.01
Category Fluency					
Unadjusted	18.8 (0.3)	16.6 (0.8)	17.5 (0.6)	15.9 (0.7)	<0.001
Adjusted[b]	17.4 (0.3)	15.8 (0.7)	17.6 (0.6)	16.0 (0.7)	0.8
Buschke Selective Reminding					
Unadjusted	7.8 (0.1)	7.2 (0.4)	7.5 (0.3)	6.6 (0.4)	0.03
Adjusted[b]	7.2 (0.2)	6.9 (0.4)	7.3 (0.4)	6.5 (0.4)	0.5
Boston Naming					
Unadjusted	14.1 (0.1)	13.4 (0.2)	13.5 (0.2)	12.9 (0.2)	<0.001
Adjusted[b]	13.6 (0.1)	13.1 (0.2)	13.4 (0.2)	13.0 (0.2)	0.6

Note: N=588. Values presented as mean (standard error).

3MS, Modofied Mini-Mental State Examination.

[a] for trend

[b] Adjusted for age, race, sex, and education

Table 4

Cognitive test scores by presence or absence of microaneurysms, hemorrhages, and hard and soft exudates

Microaneurysms and Hemorrhages	Microaneurysms		p -value	Hemorrhages		p-value
	Absent n=461	Present n=77		Absent n=446	Present n=100	
3MS	91.1 (0.4)	89.5 (1.2)	0.2	91.1 (0.4)	90.1 (1.1)	0.4
Trails A	59.5 (1.6)	69.2 (4.7)	0.04	59.8 (1.7)	62.5 (4.4)	0.6
Trails B	161.2 (4.2)	190.8 (12.3)	0.02	161.8 (4.3)	178.0 (11.5)	0.2
Category Fluency	17.3 (0.3)	15.6 (0.9)	0.06	17.3 (0.3)	16.0 (0.8)	0.1
Buschke Selective Reminding	7.2 (0.2)	6.4 (0.5)	0.1	7.2 (0.2)	7.4 (0.5)	0.6
Boston Naming	13.4 (0.1)	13.3 (0.3)	0.7	13.4 (0.1)	13.0 (0.3)	0.1

Exudates	Hard Exudates		p-value	Soft Exudates		p-value
	Absent n=513	Present n=38		Absent n=532	Present n=14	
3MS	91.0 (0.4)	92.6 (1.8)	0.3	91.0 (0.4)	90.5 (2.2)	0.8
Trails A	60.0 (1.6)	60.6 (7.0)	0.9	60.0 (1.6)	60.2 (8.7)	0.9
Trails B	162.9 (4.2)	171.6 (18.2)	0.6	163.4 (4.2)	151.2 (23.9)	0.6
Category Fluency	17.1 (0.3)	17.1 (1.3)	0.9	17.2 (0.3)	14.6 (1.6)	0.1
Buschke Selective Reminding	7.1 (0.2)	8.1 (0.8)	0.2	7.2 (0.2)	6.2 (1.0)	0.3
Boston Naming	13.4 (0.1)	13.9 (0.4)	0.2	13.4 (0.1)	13.2 (0.5)	0.7

Note: Data adjusted for age, race, sex, and education. Values are presented as mean (standard error).

3MS, Modofied Mini-Mental State Examination.