Rationale & Objective: Retinopathy and chronic kidney disease (CKD) are typically considered microvascular complications of diabetes, and cardiovascular and cerebrovascular diseases are considered macrovascular complications; however, all may share common pathological mechanisms. This study quantified the association of retinopathy with risk of kidney disease and compared with the association with cardiovascular disease in persons with diabetes.

Study Design: Retrospective cohort study.

Setting & Participants: 1,759 participants in the ARIC study who had diabetes at visit 4 and underwent retinal examination at visit 3.

Exposure: Retinopathy.

Outcome: Prevalent CKD (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m²), prevalent albuminuria (urinary albumin-creatinine ratio [UACR] > 30 mg/g), incident CKD, incident end-stage kidney disease (ESKD), incident coronary heart disease (CHD), and incident stroke.

Analytical Approach: The cross-sectional association of retinopathy with prevalent CKD and albuminuria was assessed by logistic regression. The associations between retinopathy, incident CKD, incident ESKD, incident CHD, and incident stroke were examined using Cox proportional hazards models. Seemingly unrelated regression was used to compare the strength of association between retinopathy and outcomes.

Results: During the median follow-up period of 14.2 years, 723 participants developed CKD, and there were 109 ESKD events, 399 CHD events, and 196 stroke events. Compared with the participants without retinopathy, participants with retinopathy were more likely to have reduced eGFR (OR, 1.56 [95% CI, 1.09-2.23]) and UACR > 30 mg/g (OR, 1.61 [95% CI, 1.24-2.10]). Retinopathy was associated with risk of incident CKD (HR, 1.22 [95% CI, 1.02-1.48]), ESKD (HR, 1.69 [95% CI, 1.11-2.68]), CHD (HR, 1.46 [95% CI, 1.15-1.84]), and stroke (HR, 1.43 [95% CI, 1.03-1.97]). A stronger relationship was found between retinopathy and CHD when compared with retinopathy and CKD (P = 0.03); all other associations were similar.

Limitations: Retinal examination and kidney measurements were taken at different visits.

Conclusions: The presence of retinopathy was associated with higher prevalence of kidney disease and higher risk of incident CKD, ESKD, and CHD. These results may suggest that a similar mechanism underlies the development of retinopathy and other adverse outcomes in diabetes.
As common complications of diabetes, retinopathy and kidney disease may share common underlying pathological mechanisms. This study examined the association of retinopathy and kidney disease among participants with diabetes in the Atherosclerosis Risk in Communities (ARIC) study using Cox proportional hazards models, and compared this association with the association of retinopathy and cardiovascular disease. Significant associations were observed in retinopathy with incident chronic kidney disease (CKD), end-stage kidney disease, coronary heart disease (CHD), and stroke. In addition, a stronger relationship was found between retinopathy and CHD when compared with retinopathy and CKD. These findings support the hypothesis of a relationship between retinopathy and kidney disease in diabetes, and suggest a potential linkage between retinopathy and cardiovascular complications in diabetes.

study population and assessed whether including retinopathy measurements would improve the discrimination of KFRE among persons with diabetes. Similarly, we explored whether including retinopathy measurements in the adapted Pooled Cohort Equations (PCE)—a tool to estimate atherosclerotic cardiovascular disease risk—would improve the prediction of CVD risk among persons with diabetes.

**METHODS**

**Study Population**

The ARIC Study is a prospective cohort study that recruited 15,792 participants aged 45-64 years by probability sampling from 4 US communities during 1987 to 1989. Details of the study have been published elsewhere. Follow-up examinations took place every 3 years for visit 2 in 1990-1992, visit 3 in 1993-1995, and visit 4 in 1996-1998, and the cohort was examined again for visit 5 in 2011-2013 and visit 6 in 2016-2017.

Retinal photographs were taken for 12,536 participants at visit 3. Because kidney measurements were not assessed at visit 3, we used visit 4 as our baseline. Of these participants, 11,656 returned for visit 4, among which 1,805 were defined to have prevalent diabetes. Diabetes at visit 4 was classified using the following criteria: fasting blood glucose level ≥ 126 mg/dL, nonfasting glucose level ≥ 200 mg/dL, self-reported history of diagnosis of diabetes by a physician, or use of medications for diabetes or high blood sugar in the past 2 weeks. Because of low numbers, we excluded 8 Black participants (0.4%) in Minnesota and Maryland, 5 participants (0.3%) who reported themselves to be neither White nor Black, 7 participants (0.4%) without kidney measurements, and 26 participants (1.4%) with missing data on other variables, leaving a study population of 1,759 participants. All participants provided written informed consent at each study visit. The institutional review boards at each participating institution approved the study.

**Exposure**

Details about retinopathy assessment have been published previously. In short, one 45° nonstereoscopic color retinal photograph of one eye of each participant was taken at the third visit. The eye to photograph was assigned by an algorithm to systematically achieve balance. The photographs were then assessed by masked graders in the Retinal Reading Center for retinal vascular abnormalities using the Modified Airlie House Classification of Diabetic Retinopathy. A retinopathy severity score was assigned based on the Early Treatment Diabetic Retinopathy Study severity scale. In our study, we defined categories of retinopathy as level 10, none; level 14-20, minimal (minimal nonproliferative retinopathy); level 35, mild (mild nonproliferative retinopathy); level 43+, moderate to severe (moderate to severe nonproliferative retinopathy and proliferative retinopathy).

**Outcome**

At visits 4, 5, and 6, serum creatinine was measured and used to estimate glomerular filtration rate (eGFR) with the CKD-EPI equation. Furthermore, the participants underwent active surveillance for hospitalizations and death, with International Classification of Diseases, Ninth Revision (ICD-9) and ICD-10 codes extracted from all records, and linkage to the US Renal Data System (USRDS) for identification of incident ESKD.

Baseline was considered visit 4. Prevalent CKD was defined as eGFR < 60 mL/min/1.73 m² at visit 4 and prevalent UACR as > 30 mg/g at visit 4. Among those with eGFR ≥ 60 mL/min/1.73 m² at visit 4, incident CKD was defined as (1) eGFR < 60 mL/min/1.73 m² at a subsequent visit and an eGFR decline from visit 4 of at least 25%, (2) a hospitalization or death with a kidney-related diagnostic code excluding acute kidney failure, or (3) ESKD. Among those without ESKD at visit 4, incident ESKD was defined by linkage with USRDS as previously stated. Follow-up time was calculated from the date of visit 4 to the date of an incident event or December 31, 2017, for ESKD or December 31, 2018, for incident CKD.

Cardiovascular events were identified by annual questionnaire, follow-up examinations, and the community-wide surveillance procedures. Incident coronary heart disease (CHD) was defined as fatal coronary heart disease, ascertained from death certificates, or hospitalized acute myocardial infarction, ascertained by hospital records. Stroke was identified by full hospital record abstraction. Both incident CHD and stroke events were adjudicated by physicians.
RESULTS

Baseline Characteristics
Among the 1,759 participants with diabetes included in the study population, 508 individuals (28.9%) had retinopathy. Compared with the participants without retinopathy, the participants with retinopathy were older, more likely to be Black, and were more likely to use insulin. The participants with retinopathy also had higher BP and higher fasting glucose, as well as lower eGFR and higher UACR (Table 1; Table S1).

Association of Retinopathy With Prevalence of Kidney Disease
At visit 4, there were 176 (10.0%) prevalent cases of eGFR $<60$ mL/min/1.73 m$^2$ and 389 (22.1%) cases of UACR $>30$ mg/g. In participants with retinopathy, the odds of eGFR $<60$ mL/min/1.73 m$^2$ were significantly higher than in participants without retinopathy after adjusting for risk factors (odds ratio [OR], 1.56 [95% CI, 1.09-2.23]) (Table 2). The odds of UACR $>30$ mg/g in participants with retinopathy was also higher (OR, 1.61 [95% CI, 1.24-2.10]) than in participants without retinopathy. When evaluated by category, we did not observe a dose response between severity of retinopathy and prevalent kidney disease or albuminuria (Table S2).

Association of Retinopathy With Risk of Kidney Disease
The participants were observed for a median follow-up time of 14.2 years with 723 incident CKD events and 16.2 years with 109 ESKD events (Table 3; Table S3). Figure 1 presents the unadjusted kidney-event-free survival by presence of retinopathy. By crude analysis, we observed higher risks of CKD (HR, 1.51 [95% CI, 1.28-1.77]) (Table 4) in participants with any level of retinopathy compared with the participants with no retinopathy, and the association remained statistically significant after adjusting for risk factors (HR, 1.22 [95% CI, 1.02-1.46]). When comparing among levels of retinopathy, only the mild retinopathy group showed a significantly higher hazard of CKD (HR, 1.57 [95% CI, 1.15-2.15]) (Table S4) compared with the no-retinopathy group after adjustment. Risk of CKD in minimal retinopathy (HR, 1.37 [95% CI, 0.96-1.94]) and moderate-to-severe retinopathy groups (HR, 1.09 [95% CI, 0.88-1.36]) did not show significant differences when compared with the no-retinopathy group.

Similar trends were also observed in the risk of incident ESKD when comparing the participants with retinopathy with the participants without retinopathy, with significantly higher hazards of ESKD in participants with any level of retinopathy (HR, 2.92 [95% CI, 2.00-4.25]) (Table 4) and after adjustment (HR, 1.69 [95% CI, 1.11-2.58]). Analysis by levels of retinopathy showed a significantly higher risk of ESKD in the mild retinopathy group (HR, 2.72 [95% CI, 1.52-4.87]) (Table S4) but not in the...
Table 1. Characteristic of Study Population at Baseline (Visit 4), by Presence of Retinopathy

| Characteristic | Overall | Retinopathy | No retinopathy | P  |
|---------------|---------|-------------|----------------|----|
| N             | 1,759   | 508         | 1,251          |    |
| Age, y        | 63.4 ± 5.6 | 64.2 ± 5.7 | 63.1 ± 5.5     | <0.001 |
| Female        | 900 (51.2%) | 271 (53.3%) | 629 (50.3%)    | 0.24 |
| Race/Center   |         |             |                |    |
| Whites, Forsyth Co. | 331 (18.8%) | 88 (17.3%) | 243 (19.4%) |    |
| Whites, Minneapolis | 361 (20.5%) | 75 (14.8%) | 286 (22.9%) |    |
| Whites, Washington Co. | 511 (29.1%) | 131 (25.8%) | 380 (30.4%) |    |
| Blacks, Forsyth Co. | 62 (3.5%) | 22 (4.3%) | 40 (3.2%) |    |
| Blacks, Jackson | 494 (28.1%) | 192 (37.8%) | 302 (24.1%) |    |
| BMI, kg/m²    | 31.7 ± 5.9 | 31.9 ± 6.1 | 31.6 ± 5.8     | 0.28 |
| SBP, mm Hg    | 132.3 ± 19.1 | 136.1 ± 20.0 | 130.8 ± 18.5 | <0.001 |
| DBP, mm Hg    | 70.0 ± 10.7 | 69.8 ± 10.8 | 70.1 ± 10.7    | 0.64 |
| Total cholesterol, mg/dL | 198.1 ± 41.1 | 198.4 ± 43.9 | 198.0 ± 39.9 | 0.86 |
| Fasting glucose, mg/dL | 169.4 ± 64.1 | 181.8 ± 74.4 | 164.4 ± 58.7 | <0.001 |
| Duration of diabetes, y | 8.9 ± 0.3 | 8.9 ± 0.4 | 8.9 ± 0.3      | 0.61 |
| Ever smoker   | 1,053 (59.9%) | 281 (55.3%) | 772 (61.7%) | 0.01 |
| Hypertension  | 1,144 (65.0%) | 374 (73.6%) | 770 (61.6%) | <0.001 |
| Statin use    | 306 (17.4%) | 88 (173%) | 218 (174%) | 0.96 |
| Insulin use   | 388 (22.1%) | 224 (44.1%) | 164 (131%) | <0.001 |
| eGFR, mL/min/1.73 m² | 85.9 ± 19.6 | 82.1 ± 22.6 | 875 ± 18.0 | <0.001 |
| UACR, median (p25, p75), mg/g | 5.8 (1.8, 21.4) | 8.8 (2.5, 51.1) | 5.0 (1.6, 16.0) | <0.001 |

Values for continuous variables given as mean ± standard deviation; for categorical variables, as count (percentage). P value is based on χ² test for categorical variables, t test for continuous variables, and nonparametric equality-of-medians test for medians, comparing the difference between participants with and without retinopathy.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; p25, 25th percentage; p75, 75th percentage; UACR, urinary albumin-creatinine ratio.

Table 2. Odds Ratio for Prevalent eGFR <60 mL/min/1.73 m² and Albuminuria at Visit 4, Comparing Retinopathy Versus No retinopathy

| Characteristic | Unadjusted | Adjusted |
|---------------|------------|----------|
| eGFR <60 mL/min/1.73 m² | 2.31 (1.68-3.17) | 1.56 (1.09-2.23) |
| Albuminuria ≥ 1.4 mg/g | 2.14 (1.69-2.71) | 1.61 (1.24-2.10) |

P value is calculated based on logistic regression. Adjusted models are adjusted for visit 4 variables of age, sex, race-center, body mass index, smoking status, hypertension, eGFR, total cholesterol, use of statin, fasting glucose, use of insulin, and duration of diabetes from visit 1 to visit 4.

Table 3. Number of Participants at Risk and Number of Incident Outcome Events During Follow-up Period

| Outcome | Overall | No of Events (%) | No retinopathy | Retinopathy |
|---------|---------|------------------|----------------|-------------|
|         | No. at Risk | No. of Events | No. at Risk | No. of Events | No. at Risk | No. of Events |
| CKD     | 1,582 | 723 (45.7) | 1,155 | 514 (44.5) | 427 | 209 (48.9) |
| ESKD    | 1,752 | 109 (6.2) | 1,247 | 55 (4.4) | 505 | 54 (10.7) |
| CHD     | 1,469 | 399 (27.2) | 1,068 | 268 (25.1) | 401 | 131 (32.7) |
| Stroke  | 1,693 | 196 (11.6) | 1,216 | 124 (10.2) | 477 | 72 (15.1) |

Participants were observed for a maximum of 21.9 years, with a median follow-up time of 14.2 years for incident CKD, 16.2 years for incident ESKD, 14.8 years for incident CHD, and 15.8 years for incident stroke.

Abbreviations: CKD, chronic kidney disease; ESKD, end-stage kidney disease; CHD, coronary heart disease; CKD, chronic kidney disease; ESKD, end-stage kidney disease.

minimal retinopathy (HR, 1.09 [95% CI, 0.33-3.57]) or moderate-to-severe retinopathy (HR, 1.48 [95% CI, 0.91-2.40]) groups.

Association of Retinopathy With Risk of Cardiovascular Disease and Assessing Strength of Association

The participants were observed for a median follow-up time of 14.8 years with 399 incident CHD events and 15.8 years with 196 stroke events. Figure 2 presents the unadjusted CHD- and stroke-free survival by presence of retinopathy.

Compared with the participants without retinopathy, the participants with retinopathy had a higher risk of CHD (HR, 1.46 [95% CI, 1.15-1.84]) and stroke (HR, 1.43 [95% CI, 1.03-1.97]) after fully adjusting for risk factors. When comparing by level of retinopathy, higher risk of CHD was observed in participants with minimal retinopathy (HR, 1.79 [95% CI, 1.16-2.78]) (Table S4) and moderate-to-severe retinopathy (HR, 1.39 [95% CI, 1.06-1.82]), while higher risk of stroke was observed in...
Fig. 1. Survival curves of (A) CKD and (B) ESKD in participants, by presence versus absence of retinopathy. Survivor function graphs are based on Cox proportional hazards model. Models are adjusted for visit 4 variables of age, sex, race and center, BMI, smoking status, hypertension, eGFR, UACR, total cholesterol, use of statin, fasting glucose, use of insulin, and duration of diabetes from visit 1 to visit 4. Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; UACR, urinary albumin-creatinine ratio.

Discussion
In our study of 1,759 persons with diabetes, the presence of retinopathy was a robust risk factor not only for kidney outcomes but also CHD and stroke. The association between CHD and retinopathy was stronger than that between CKD and retinopathy, with no evidence for a dose response between the severity of retinopathy and adverse kidney outcomes. Our study also showed good discrimination of the 4 variables in the KFRE for predicting ESKD risk in this population of patients with diabetes, and including retinopathy did not improve the discrimination.

Our finding of an association between retinopathy and kidney disease is consistent with previous studies in other populations of adults with diabetes. It has been reported that the kidney and eye share a similar structure of the vascular networks, developmental pathways, and pathological progression. Pleiotropic roles of Pax, WT1, BMP7, and Notch2 genes in kidney and eye development as well as pathologic deterioration have been noted. There are many common pathologic mechanisms for kidney and eye diseases, including atherosclerosis, endothelial dysfunction, oxidative stress, and inflammation.

An interesting aspect of our study was the stronger association between retinopathy and CHD than retinopathy and kidney outcomes. This is seemingly contrary to conventional wisdom, in which the presence of retinopathy has been thought to be a necessary precursor to the development of kidney disease. On the other hand, retinal microvascular impairment has also been reported to predict cardiovascular disease. Additional studies should evaluate the timing of the onset of retinopathy with the development of CHD. Interestingly, we found that the presence of retinopathy had no additional predictive power over and above eGFR, UACR, age, and sex for the development of ESKD. Similarly, the inclusion of

Table 4. Hazards Ratio for Incident CKD, ESKD, CHD, and Stroke, Comparing Retinopathy Versus No Retinopathy

|           | Unadjusted HR (95% CI) | P     | Adjusted HR (95% CI) | P     |
|-----------|------------------------|-------|----------------------|-------|
| CKD       | 1.51 (1.28-1.77)       | <0.001| 1.22 (1.02-1.46)     | 0.03  |
| ESKD      | 2.92 (2.00-4.25)       | <0.001| 1.69 (1.11-2.58)     | 0.01  |
| CHD       | 1.54 (1.25-1.90)       | <0.001| 1.46 (1.15-1.84)     | 0.002 |
| Stroke    | 1.78 (1.33-2.38)       | <0.001| 1.43 (1.03-1.97)     | 0.03  |

P value is calculated based on Cox proportional hazards model. Adjusted models are adjusted for visit 4 variables of age, sex, race and center, body mass index, smoking status, hypertension, estimated glomerular filtration rate, urinary albumin-creatinine ratio, total cholesterol, use of statin, fasting glucose, use of insulin and duration of diabetes from visit 1 to visit 4.

Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; ESKD, end-stage kidney disease; HR, hazards ratio.
retinopathy in CVD risk prediction did not help improve discrimination.

The strengths of our study include the large sample size and long follow-up period, as well as the detailed measurements of risk factors at each examination. One limitation is that the retinal photographs and kidney measurements were taken at different visits. Retinal examinations were only taken in 1 eye of each participant, and a proportion (~16%) of the photographs were ungradable, which may have resulted in misclassification and underestimation of retinopathy cases.9,11,12,20,21,40,41 Survival bias is also a concern. Among participants who have diabetes at visit 3, those with retinopathy were less likely to attend visit 4 compared with those without retinopathy (P = 0.002).

The development of kidney disease was assessed overall, and not kidney disease solely attributable to diabetes. The results may not represent the associations in persons who are not Black or White. Additionally, the small sample size of those with minimal (N = 90) or mild retinopathy (N = 121) might limit the power of the analysis.

In conclusion, our study indicates that retinopathy is associated with an elevated risk of kidney disease and cardiovascular disease in persons with diabetes. These findings support the hypothesis of microvascular pathology underlying progression of kidney and cardiovascular disease, and might suggest that prevention and early diagnosis of microvascular disease could improve other clinical outcomes in diabetes. Further studies are needed to validate our findings on the strength of relationship between retinopathy, kidney disease, and cardiovascular disease.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Characteristic of study population at baseline (visit 4), by presence of retinopathy categories.

Table S2: Number of participants at risk and number of incident outcome events during follow-up period.

Table S3: Adjusted odds ratio for prevalent eGFR <60 mL/min/1.73 m² and albuminuria at visit 4, comparing levels of retinopathy versus no retinopathy.

Table S4: Adjusted hazards ratio for incident kidney disease, ESKD, coronary heart disease and stroke, comparing levels of retinopathy versus no retinopathy.

ARTICLE INFORMATION

Authors’ Full Names and Academic Degrees: Jingyao Hong, MHS, Aditya Surapaneni, PhD, Natalie Daya, MPH, Elizabeth Selvin, PhD, MPH, Josef Coresh, MD, PhD, Morgan E. Grams, MD, PhD, and Shoshana H. Ballew, PhD.

Authors’ Affiliations: Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

Address for Correspondence: Shoshana H Ballew, PhD, 2024 East Monument St, Baltimore, MD 21205. Email: sballew1@jhmi.edu

Authors’ Contributions: Study concept and design: JH, MEG, SHB; data analysis and interpretation: JH, AS, ND, SHB; supervision/mentorship: JH, SHB. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Support: This study used data collected by the Atherosclerosis Risk in Communities (ARIC) Study. The ARIC study has been funded in whole or in part with federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under contract nos. HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, and HHSN 268201700004I.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Acknowledgements: The authors thank the staff and participants of the ARIC Study for their important contributions.
Peer Review: Received December 23, 2020, as a submission to the expedited consideration track with 2 external peer reviews. Direct editorial input from the Statistical Editor and the Editor-in-Chief. Accepted in revised form April 14, 2021.

REFERENCES
1. International Diabetes Federation. IDF Diabetes Atlas. 8th ed. International Diabetes Federation; 2017.
2. World Health Organization. Global Report on Diabetes. WHO; 2016.
3. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; 2017.
4. United States Renal Data System. 2016 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2016.
5. Kang D, Kannelis J, Hugo C, et al. Role of the microvascular endothelium in progressive renal disease. J Am Soc Nephrol. 2002;13(3):806-816. https://doi.org/10.1681/ASN.2001338006
6. Park Y, Shin JA, Han J, Park Y, Yim HW. The association between chronic kidney disease and diabetic retinopathy: the Korea National Health and Nutrition Examination Survey 2008-2010. PLoS One. 2015;10(4):e0125338. https://doi.org/10.1371/journal.pone.0125338
7. Rodríguez-Poncelas A, Mundet-Tudurí X, Miravet-Jímenez S, et al. Chronic kidney disease and diabetic retinopathy in patients with type 2 diabetes. PLoS One. 2016;11(2):e0149448. https://doi.org/10.1371/journal.pone.0149448
8. Penno G, Solini A, Zoppini G, et al. Rate and determinants of association between advanced retinopathy and chronic kidney disease in patients with type 2 diabetes. Diabetes Care. 2012;35(11):2317-2323. https://doi.org/10.2337/dc12-0628
9. Cheung N, Wang JJ, Klein R, Couper DJ, Sharrett AR, Wong TY. Diabetic retinopathy and the risk of coronary heart disease. Diabetes Care. 2007;30(7):1742-1746. https://doi.org/10.2337/dc07-0264
10. Klein R, Marino EK, Kuller LH, et al. The relation of atherosclerotic cardiovascular disease to retinopathy in people with diabetes in the Cardiovascular Health Study. Br J Ophthalmol. 2002;86(1):84-90. https://doi.org/10.1136/bjo.86.1.84
11. Liew G, Campbell S, Klein R, et al. Ten-year longitudinal changes in retinal microvascular lesions: the Atherosclerosis Risk in Communities Study. Ophthalmology. 2011;118(8):1612-1618. https://doi.org/10.1016/j.jfdi.2011.01.003
12. Seidelmann SB, Brian C, Bravo PE, et al. Retinal vessel calibers in predicting long-term cardiovascular outcomes. Circulation. 2016;134(18):1329-1338. https://doi.org/10.1161/CIRCULATIONAHA.116.032425
13. Sawhney S, Beaulieu M, Black C, et al. Predicting kidney failure risk after acute kidney injury among people receiving nephrology clinic care. Nephrol Dial Transplant. 2020;35(5):836-845. https://doi.org/10.1093/ndt/gfy294
14. Akbari S, Knoll G, White CA, Kumar T, Fairhead T, Akbari A. Accuracy of kidney failure risk equation in transplant recipients. Kidney Int Rep. 2019;4(9):1334-1337. https://doi.org/10.1016/j.ekir.2019.05.009
15. Major RW, Shepherd D, Medcalf JF, Xu G, Gray LJ, Brunskill NJ. The kidney failure risk equation for prediction of end stage renal disease in UK primary care: an external validation and clinical impact projection cohort study. PLOS Med. 2019;16(11):e1002955. https://doi.org/10.1371/journal.pmed.1002955
16. Whitlock RH, Chartier M, Komenda P, et al. Validation of the kidney failure risk equation in Manitoba. Can J Kidney Health Dis. 2017;4. https://doi.org/10.1177/2054358117705372
17. Winnicki E, McCulloch CE, Mitsnese MM, Furth SL, Warady BA, Ku E. Use of the kidney failure risk equation to determine the risk of progression to end-stage renal disease in children with chronic kidney disease. JAMA Pediatr. 2018;172(2):174-180. https://doi.org/10.1001/jamapediatrics.2017.4083
18. Muntrer P, Colantonio LD, Cushman M, et al. Validation of the atherosclerotic cardiovascular disease pooled cohort risk equations. JAMA. 2014;311(14):1406-1415. https://doi.org/10.1001/jama.2014.2630
19. ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. Am J Epidemiol. 1989;129(4):687-702. https://doi.org/10.1093/oxfordjournals.aje.a115184
20. Wong TY, Klein R, Amirul Islam FM, et al. Three-year incidence and cumulative prevalence of retinopathy: the Atherosclerosis Risk in Communities Study. Am J Ophthalmol. 2007;143(6):970-976. https://doi.org/10.1016/j.ajo.2007.02.020
21. Wong TY, Coresh J, Klein R, et al. Retinal microvascular abnormalities and renal dysfunction: the Atherosclerosis Risk in Communities Study. J Am Soc Nephrol. 2004;15(9):2469-2476. https://doi.org/10.1073/pnas.0000136133.28194. E4
22. ARIC Exam 4 Derived Variable Dictionary, Version 46. September 2010. https://sites.cscw.unc.edu/aris/sites/default/files/public/manuals/DERIVE46.pdf
23. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the atherosclerosis risk in communities study. Ophthalmology. 1999;106(12):2269-2280. https://doi.org/10.1016/S0161-6420(99)90525-0
24. Klein R, Sharrett AR, Klein BEK, et al. The association of atherosclerosis, vascular risk factors, and retinopathy in adults with diabetes: the atherosclerosis risk in communities study. Ophthalmology. 2002;109(7):1225-1234. https://doi.org/10.1016/s0161-6420(02)01074-6
25. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy: ETDRS report number 12. Ophthalmology. 1991;98(5 Suppl):823-833. https://doi.org/10.1016/S0161-6420(91)38014-2
26. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612. https://doi.org/10.7326/0003-4819-150-9-20090905050-00006
27. Bash LD, Coresh J, Köttgen A, et al. Defining incident chronic kidney disease in the research setting: the ARIC Study. Am J Epidemiol. 2009;170(4):414-424. https://doi.org/10.1093/aje/kwp151
28. Rebholz CM, Coresh J, Ballew SH, et al. Kidney failure and ESRD in the Atherosclerosis Risk in Communities (ARIC) Study: comparing ascertainment of treated and untreated kidney failure in a cohort study. Am J Kidney Dis. 2015;66(2):231-239. https://doi.org/10.1053/j.ajkd.2015.01.016
29. White AD, Folsom AR, Chambless LE, et al. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years experience. J Clin Epidemiol. 1996;49(2):223-233. https://doi.org/10.1016/0895-4356(95)00041-0
30. ARIC Research Group. Atherosclerosis Risk in Communities Study Protocol. Manual 2. Cohort Component Procedures.
31. Zellner A. An efficient method of estimating seemingly unrelated regressions and tests for aggregation bias. *J Am Stat Assoc*. 1962;57(298):348-368. https://doi.org/10.2307/2281644

32. Grunwald JE, Pistilli M, Ying G, et al. Retinopathy and progression of CKD: the CRIC Study. *Clin J Am Soc Nephrol*. 2014;9(7):1217-1224. https://doi.org/10.2215/CJN.11761113

33. Hwang HS, Kim SY, Hong YA, et al. Clinical impact of coexisting retinopathy and vascular calcification on chronic kidney disease progression and cardiovascular events. *Nutr Metab Cardiovasc Dis*. 2016;26(7):590-596. https://doi.org/10.1016/j.numecd.2016.02.005

34. Leisy HB, Rastogi A, Guevara G, Ahmad M, Smith RT. The association of geographic atrophy and decreased renal function in patients with age-related macular degeneration. *Eye*. 2017;31(1):62-67. https://doi.org/10.1038/eye.2016.261

35. He F, Xia X, Wu XF, Yu XQ, Huang FX. Diabetic retinopathy in predicting diabetic nephropathy in patients with type 2 diabetes and renal disease: a meta-analysis. *Diabetologia*. 2013;56(3):457-466. https://doi.org/10.1007/s00125-012-2796-6

36. Mottl AK, Kwon KS, Garg S, Mayer-Davis EJ, Klein R, Kshirsagar AV. The association of retinopathy and low GFR in type 2 diabetes. *Diabetes Res Clin Pract*. 2012;98(3):487-493. https://doi.org/10.1016/j.diabres.2012.09.041

37. Zhang H, Wang J, Ying G, Shen L, Zhang Z. Diabetic retinopathy and renal function in Chinese type 2 diabetic patients. *Int Urol Nephrol*. 2014;46(7):1375-1381. https://doi.org/10.1007/s11255-014-0675-4

38. Izzedine H, Bodaghi B, Launay-Vacher V, Deray G. Eye and kidney: from clinical findings to genetic explanations. *J Am Soc Nephrol*. 2003;14(2):516-529. https://doi.org/10.1097/01.ASN.0000051705.97966.ad

39. Wong CW, Wong TY, Cheng C, Sabanayagam C. Kidney and eye diseases: common risk factors, etiological mechanisms, and pathways. *Kidney Int*. 2014;85(6):1290-1302. https://doi.org/10.1038/ki.2013.491

40. Sahli MW, Mares JA, Meyers KJ, et al. Dietary intake of lutein and diabetic retinopathy in the Atherosclerosis Risk in Communities Study (ARIC). *Ophthalmic Epidemiol*. 2016;23(2):99-108. https://doi.org/10.3109/09286586.2015.1129426

41. Selvin E, Ning Y, Steffes MW, et al. Glycated hemoglobin and the risk of kidney disease and retinopathy in adults with and without diabetes. *Diabetes*. 2011;60(1):298-305. https://doi.org/10.2337/db10-1198
# Is retinopathy associated with higher risk of incident CKD, ESKD, and CHD in a diabetic population?

## Demographics

| ARIC study cohort | Retrospective | N = 1759 |
|-------------------|---------------|----------|

## Exposure

| Retinal examination | Diabetes |
|---------------------|----------|
| No Retinopathy      | Ref      |
| Retinopathy         | Ref      |

## Results

| Prevalence of CKD | Ref | Ref |
|-------------------|-----|-----|
| Albininuria       |     |     |

| Cumulative Incidence of CKD | Ref | Ref |
|------------------------------|-----|-----|
| ESKD                         |     |     |
| CHD                          |     |     |
| Stroke                       |     |     |

Follow up ≤ 21.9 yrs

| No Retinopathy | Ref | Ref | 44.5% | 4.4% | 25.1% | 10.2% |
|----------------|-----|-----|-------|------|-------|-------|
| Adjusted Odds ratio (95% CI) | 1.22 (1.02 - 1.46) | 1.69 (1.11 - 2.58) | 1.46 (1.15 - 1.84) | 1.43 (1.03 - 1.97) |

| Retinopathy | 1.56 | 1.61 |
|            | [1.09 - 2.23] | [1.24 - 2.10] |

| CHD | 48.9% | 10.7% | 32.7% | 15.1% |

## Reference

Hong J, Surapari N, Daya N et al. Retinopathy and risk of kidney disease in persons with diabetes. *Kidney Medicine*, 2021.

Visual Abstract by Sai Sudha Manmooli, MD, FAAP

@drS_M_Sudha