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Retinopathy and CKD as Predictors of All-Cause and Cardiovascular Mortality: National Health and Nutrition Examination Survey (NHANES) 1988–1994

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Abstract

Background—Retinopathy is associated with increased mortality risk in general populations. We evaluated the joint effect of retinopathy and chronic kidney disease (CKD) on mortality in a representative sample of US adults.

Study Design—Prospective cohort study.

Setting & Participants—7,640 adults from the National Health and Nutrition Examination Survey (NHANES) 1988–1994 with mortality linkage through 12/31/2006.

Predictors—CKD, defined as low estimated glomerular filtration rate (eGFR; <60 ml/min/1.73 m^2) or albuminuria (urine protein-creatinine ratio ≥30mg/g), and retinopathy, defined as presence of microaneurysms, hemorrhages, exudates, microvascular abnormalities, or other evidence of diabetic retinopathy by fundus photograph.

Outcomes—All-cause and cardiovascular mortality.

Measurements—Multivariable-adjusted Cox proportional hazards.

Results—Overall, 4.6% of participants had retinopathy and 15% had CKD. Mean age was 56 years, 53% were women and 81% non-Hispanic white. Prevalence of retinopathy in CKD was 11%. We identified 2,634 deaths during 14.5 years' follow-up. In multivariable analyses, compared with individuals with neither CKD nor retinopathy, the HRs for all-cause mortality were 1.02 (95% CI, 0.75–1.38), 1.52 (95% CI, 1.35–1.72), and 2.39 (95% CI, 1.77–3.22) for individuals with retinopathy only, for those with CKD only, and for those with both CKD and retinopathy, respectively. Corresponding HRs for cardiovascular mortality were 0.96 (95% CI, 0.50–1.84),

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1.72 (95% CI, 1.47–2.00) and 2.96 (95% CI, 2.11–4.15), respectively. There was a significant synergistic interaction between retinopathy and CKD on all-cause mortality (p=0.04).

Limitations—Presence of retinopathy was evaluated only once. Small sample size of some of the subpopulations studied.

Conclusions—In the presence of CKD, retinopathy is a strong predictor of mortality in this adult population.

Index Words

chronic kidney disease (CKD); retinopathy; fundus pathology; funduscopy; mortality; cardiovascular disease; death; renal failure

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It is estimated that over 26 million individuals in the United States have chronic kidney disease (CKD).[1] CKD is an independent risk factor for cardiovascular disease (CVD) and it is well known that individuals with CKD are at increased risk of cardiovascular morbidity and mortality.[2;3] The mechanism of increased cardiovascular risk in CKD is not fully understood but is likely due to increased burden of traditional and nontraditional CVD risk factors.[4]

In non-CKD populations, retinopathy has been associated with increased risk of death in persons with and without diabetes.[5–7] Retinopathy has not been well characterized in the CKD population. Recently it has become apparent that fundus pathology is quite prevalent in individuals with CKD,[8–10] and has been associated with prevalent CVD and cognitive dysfunction[8;11;12] A funduscopic examination offers a noninvasive evaluation of systemic microvascular disease. Several studies have reported correlations between retinopathy and kidney disease in individuals with and without diabetes.[13–15] However, the association between retinopathy and mortality has not been evaluated in this particular population. A funduscopic examination may prove to be a helpful tool in predicting mortality in persons with CKD.

In this study, we used data from the Third National Health and Nutrition Examination Survey (NHANES III), 1998–1994, a nationally representative sample of the U.S. population, to examine the joint effect of retinopathy and CKD on cardiovascular and all-cause mortality. We hypothesized that individuals with either retinopathy or CKD will have increased mortality compared with participants with neither condition, and that individuals with both retinopathy and CKD will have the highest mortality risk.

METHODS

Study Population and Baseline Data

The NHANES III was conducted by the National Center for Health Statistics (NCHS) between 1988 and 1994 using a stratified, clustered, multistage probability sample survey design of the civilian, noninstitutionalized US population with oversampling of blacks and Mexican Americans. The survey protocol was approved by the NCHS institutional review board. All participants provided informed consent.

There were 9,239 participants aged ≥40 years who were interviewed at home for sociodemographic and medical history and had one eye photographed at a mobile examination center (MEC).[16;17] Of those, 395 participants with fundus photograph ungradable for diabetic retinopathy and 639 participants with missing fundus photograph data were excluded. In addition, 565 participants were excluded due to missing serum creatinine or urine albumin-creatinine ratio (ACR) data, resulting in 7640 individuals available for analyses. Compared with participants who were included in these analyses, those excluded were similar in age and gender; more likely to be non-Hispanic black and smokers; and more likely to have low income, less than high school education, and higher prevalence of albuminuria, CVD and diabetes.

Blood pressure (BP), and blood and urine samples were obtained during the 4-hr MEC physical examination. Hypertension was defined as systolic BP >140 mmHg or diastolic BP >90 mmHg or the use of antihypertensive medications. Diabetes was defined as a history of diabetes, use of insulin or other medication to treat diabetes, a fasting blood glucose level ≥126 mg/dL, or a random blood glucose level ≥200 mg/dL. For stratified analyses by diabetes status using the above definition, we identified 1142 participants with and 6482 without evidence of diabetes.

Exposure Ascertainment: Retinopathy and CKD

As part of the NHANES III protocol, a non-stereoscopic, color, 45-degree photograph of the ocular fundus centered between the optic nerve and the macula of one randomly selected eye was taken in the MEC on examinees aged ≥ 40 years by a trained examiner. The camera used was a Canon CR4–45NM “non-mydriatic” fundus camera (Canon USA, Lake Success, New York, NY). The exposed film was mailed to the University of Wisconsin-Madison, Department of Ophthalmology, where it was processed by a local laboratory into transparencies that were evaluated for photographic quality and grading. The grading system used for classifying diabetic retinopathy was based on a modification of the Airlie House classification scheme.[18] Additional information can be found on the NHANES III website.[19] For this study, retinopathy was defined as the presence of any of the following: soft/hard exudates, intraretinal microvascular abnormalities, hemorrhages, microaneurysms, early/moderate/severe non-proliferative diabetic retinopathy, fibrous proliferation, proliferative diabetic retinopathy or other evidence of diabetic retinopathy. Of the 7640 participants included in this study, 494 were coded as having any type of retinopathy and 7146 as having no retinopathy.

CKD was defined by either an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2, using the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation, which was developed from the pooling of several cohorts with GFR measured by iothalamate;[20] or the presence of albuminuria (urine ACR ≥30mg/g). In NHANES III, serum creatinine was measured using a modified Jaffé reaction and standardized. We used the formula for correction of serum creatinine recommended in the NHANES III Data File Documentation.[21] Urine albumin and creatinine concentrations were measured in one random urine sample. Urine albumin was measured using a solid-phase fluorescent immunoassay, with intra-assay and inter-assay coefficients of variation, 8%.[22]

Outcome Ascertainment

Vital status was determined using the NHANES III Public-use Linked Mortality File which provides vital status follow-up data in person-months from the date of the NHANES III survey participation through the date of death or December 31, 2006. Mortality was ascertained by the NCHS through a probabilistic match between NHANES III participants and National Death Index death certificate records. Participants who were not matched with any death records were considered to be alive through the follow-up period. The cause of death was assigned by the NCHS based on the 10th revision of the International Classification of Diseases (*ICD-10*).[23;24] For this study, cardiovascular mortality was defined as deaths due to diseases of the heart, essential hypertension and hypertensive kidney disease, cerebrovascular disease, atherosclerosis, and other diseases/disorders of the circulatory system (codes I00–I99).

Statistical Methods

The NCHS recommendations were followed to account for stratification and clustering of the survey design, as well as oversampling of ethnic minorities and elderly persons.[25] Continuous variables were expressed as means ± standard error or medians (interquartile range) if not normally distributed; and categorical variables as weighted percentage. Baseline differences in demographic and clinical characteristics were tested using the χ^2 test for categorical variables and *t* test for continuous variables. Cox proportional hazards models were used to evaluate the joint effect of retinopathy and CKD on all-cause and cardiovascular mortality adjusting for important covariates known to be associated with the predictors and outcomes of interest, including age, gender, race/ethnicity, education, annual family income, smoking status, hypertension, hemoglobin A1c, diabetes, CVD, family history of coronary heart disease, body mass index and total cholesterol. We conducted formal tests for interaction by including a retinopathy-CKD interaction term in addition to the main effects to the fully-adjusted models for all-cause and cardiovascular mortality. Additional multivariable analyses were conducted to evaluate the joint effect of retinopathy with albuminuria (ACR ≥30 mg/g), and of retinopathy with low eGFR (<60 ml/min/1.73 m^2) on outcomes; these models included the variables already listed in addition to eGFR and natural log of ACR, respectively. Formal tests for interaction were also conducted for retinopathy-albuminuria and retinopathy–low eGFR joint effect. Stratified analyses by CKD status and diabetes status were also conducted. Due to missing values in at least one of the covariates included in the fully-adjusted models, 483 participants were excluded from multivariable analyses. All tests were two-sided, and $p<0.05$ was considered significant for hypothesis testing. The proportional hazards assumption of the Cox models was examined using Schoenfeld residuals, which showed no significant departure from proportionality over time ($p >0.05$).[26] Analyses were performed with SAS 9.3 (SAS Institute Inc, Cary, NC) and SAS-Callable SUDAAN 10.0.1 (RTI International, Research Triangle Park, NC).

RESULTS

Participant Characteristics

The overall weighted prevalence of retinopathy was 4.6%. The weighted prevalence of retinopathy was 11.0% among participants with CKD (25% and 6% in those with and

without diabetes, respectively), and 3.7% in individuals without CKD. The weighted prevalence of CKD was 15%. Demographic and clinical characteristics of participants overall and by CKD and retinopathy status are presented in Table 1. The mean age was 56 years, 53% of participants were women and 81% non-Hispanic white. Among individuals with CKD, those with retinopathy (vs. no retinopathy) were more likely to be non-Hispanic black (17.8% vs. 10.6%) or Mexican American (6.4% vs. 2.8%) and to have ACR > 300 mg/g (15.1% vs. 8.4%), diabetes (58.9% vs. 22.6%), and higher systolic BP (147.1 vs. 141.0 mmHg). Among participants without CKD, those with retinopathy (vs. no retinopathy) were more likely to be older (56.3 vs. 54.3 years) and to have annual income <$20,000 (34.9% vs. 26.7%), lower eGFR (88.7 vs. 91.9 ml/min/1.73 m^2), and to have a diagnosis of hypertension (49.1% vs. 33.7%) or diabetes (30.6% vs. 6.5%),

Association Between Retinopathy and Mortality

Over a median follow-up period of 14.5 years, 2634 deaths occurred, of which 1165 were due to a cardiovascular cause. The number of all-cause and cardiovascular mortality events, weighted event rates, and hazard ratios (HRs) with 95% confidence intervals (CIs) for each combination of predictors are summarized in Table 2. For the outcome of all-cause mortality, there was a significant interaction between retinopathy and CKD (p=0.04) and between retinopathy and albuminuria (p=0.009). For the outcome of cardiovascular mortality, there was a significant interaction between retinopathy and albuminuria (p=0.04). Results similar to those obtained in the overall cohort were observed in multivariable regression analyses stratified by diabetes status. Among diabetics, using individuals with neither retinopathy nor CKD as the reference group, the HRs for all-cause mortality were 0.78 (95% CI, 0.67–1.66), 1.43 (95% CI, 1.08–1.89), and 2.53 (95% CI, 1.53–4.19) for individuals with retinopathy only, for participants with CKD only, and for those with both retinopathy and CKD, respectively. Among participants without diabetes, the corresponding HRs were 1.16 (95% CI, 0.81–1.67), 1.55 (95% CI, 1.36–1.77), and 2.06 (95% CI, 1.28–3.33), respectively. Furthermore, in regression analyses limited to participants with CKD (adjusting for the same variables as in the analyses presented in Table 2, in addition to natural log ACR and CKD-EPI eGFR), the HRs of all-cause and cardiovascular mortality among individuals with retinopathy (vs. no retinopathy) were 1.52 (95% CI, 1.08–2.16) and 1.72 (95% CI, 1.11–2.65), respectively. In analyses limited to participants without CKD, the HRs of all-cause and cardiovascular mortality among individuals with retinopathy (vs. no retinopathy) were 1.03 (95% CI, 0.74–1.43) and 0.89 (95% CI, 0.47–1.70), respectively.

DISCUSSION

Although previous studies have examined the association of retinopathy and mortality in non-CKD populations, to our knowledge, this study is the first to examine the joint effect of retinopathy and CKD on mortality. Compared with individuals with neither retinopathy nor CKD, the presence of both retinopathy and CKD was associated with more than a two-fold increase in all-cause and cardiovascular mortality independent of demographic and clinical factors including smoking, hypertension and history of CVD, indicating that retinopathy may provide additional information regarding cardiovascular risk. Similar results were obtained when albuminuria and low eGFR were analyzed separately. The association

between retinopathy and mortality remained significant when analyses were restricted to individuals with CKD.

We found a prevalence of retinopathy of 11% in individuals with CKD and 3.7% in individuals without CKD. This prevalence is lower than the 25% prevalence of retinopathy (diabetic, hypertensive or other retinopathy) reported by Grunwald *et al* in the Chronic Renal Insufficiency Cohort (CRIC) Study.[8] The difference in prevalence is likely related to the greater severity of CKD in the CRIC Study, in which the mean eGFR was 44.6 ml/min/1.73 m^2. Additionally, funduscopic photographs were done of only one eye in NHANES III participants, which may underestimate the prevalence of retinopathy. Similar to findings from the CRIC Study, we found retinopathy to be more common among racial/ethnic minorities and in participants with self-reported CVD, hypertension and diabetes.

Only a few studies have examined the prognostic significance of retinopathy in CKD. Prior studies have reported an association between retinopathy and incident CKD, and CKD progression;[14;15] however the association between mortality and retinopathy in individuals with CKD has not been previously evaluated to our knowledge. In our study, retinopathy was a significant predictor of mortality in CKD. In addition, we observed a significant joint effect of retinopathy and CKD on outcomes. Mechanisms underlying these associations are not known but potential explanations include microvascular damage associated with aging, hypertension, atherosclerosis and other vascular and endothelial changes that might be present in the retina and other vascular beds such as the heart, brain and kidneys.[28] In contrast to prior studies,[6;27] we did not find a significant association between retinopathy and mortality in individuals without CKD. Reasons for this difference are unclear, but it is possible that, due to the low prevalence of retinopathy among individuals without CKD in our study, there was not enough power to detect this association. Additionally, as mentioned earlier, photography of only one eye may have contributed to an underestimation of the prevalence of retinopathy in the non-CKD subpopulation.

Strengths of this study include a large sample size, prospective design with a median follow up of 14.5 years, and standardized fundus photograph grading system. However, our study has several weaknesses. First, the presence of both predictors, retinopathy and CKD, was evaluated only once, which might lead to misclassification. Second, individuals excluded from the analysis because of missing data on fundus photograph, serum creatinine or urine ACR had significantly different demographic and clinical characteristics and this could have led to selection bias, which could in turn lead to erroneous inferences regarding the association between retinopathy and mortality. Third, because of the study design, there is always the possibility of residual confounding and causality cannot be established. Lastly, some of the subpopulations studied had small sample sizes, which explained the wide CIs for the corresponding parameter estimates.

In summary, we found that retinopathy is strongly associated with all-cause and cardiovascular death in individuals with CKD and that the presence of both CKD and retinopathy confers a heightened risk of adverse outcomes. These findings suggest that future work is needed to evaluate retinopathy screening in CKD as a noninvasive tool for assessment of cardiovascular risk in this population.

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Table 1

Characteristics of NHANES III Participants by Presence of CKD and Retinopathy

Variable	Overall (N=7640)	CKD			No CKD		
		Retinopathy (n=220)	No Retinopathy (n=1370)	*P*	Retinopathy (n=274)	No Retinopathy (n=5776)	*P*
Age (y)	56.1 (0.4)	65.1 (1.3)	65.5 (0.8)	0.8	56.3 (0.9)	54.3 (0.4)	0.04
Female sex	3960 (53.2%)	136 (62.8%)	701 (55.6%)	0.2	118 (46.6%)	3005 (52.8)	0.2
Race/ethnicity							
Non-Hispanic White	3799 (81.3%)	80 (71.1%)	749 (80.3%)	0.004	118 (79.9%)	2852 (81.7%)	0.2
Non-Hispanic Black	1792 (8.6%)	68 (17.8%)	329 (10.6%)		73 (10.7%)	1322 (8.0%)	
Mexican American	1747 (3.4%)	66 (6.4%)	249 (2.8%)		77 (5.0)	1355 (3.4%)	
Other	302 (6.6%)	6 (4.7%)	43 (6.3%)		6 (4.4%)	247 (6.8%)	
Annual family income <$20,000	3481 (30.3%)	138 (48.1%)	806 (48.4%)	0.9	134 (34.9%)	2403 (26.7%)	0.03
<High school education	3400 (27.7%)	134 (45.1%)	744 (40.0%)	0.3	134 (33.0%)	2388 (25.1%)	0.03
eGFR (ml/min/1.73 m^2)	88.7 (0.4)	72.4 (2.1)	71.3 (1.2)	0.7	88.7 (1.1)	91.9 (0.4)	0.008
Urine ACR							
<30 mg/g	6536 (89.5%)	38 (27.4%)	448 (32.7%)	0.03	100	100	
30 – <300 mg/g	908 (9.1%)	119 (57.5%)	789 (58.9%)				
≥300 mg/g	196 (1.4%)	63 (15.1%)	133 (8.4%)				
Current Smoker	1742 (23.1%)	35 (20.1%)	260 (19.2%)	0.9	67 (23.9%)	1380 (23.8%)	0.9
Hypertension	3608 (39.7%)	178 (75.8%)	989 (68.9%)	0.2	143 (49.1%)	2298 (33.7%)	<0.001
CVD*	898 (9.0%)	51 (21.5%)	317 (18.7%)	0.5	33 (9.3%)	497 (7.1%)	0.3
Diabetes mellitus	1142 (10.3%)	149 (58.9%)	343 (22.6%)	<0.001	105 (30.6%)	545 (6.5%)	<0.001
Family history of premature CHD†	717 (11.4%)	25 (16.6%)	137 (12.2%)	0.3	21 (6.4%)	534 (11.3%)	0.06
Systolic BP (mmHg)	128.8 (0.4)	147.1 (2.5)	141.0 (0.8)	0.01	132.1 (1.4)	126.2 (0.4)	<0.001
Diastolic BP (mmHg)	76.3 (0.2)	76.5 (1.2)	77.8 (0.5)	0.3	77.8 (1.0)	76.0 (0.2)	0.08
Body Mass Index (kg/m^2)	27.3 (0.1)	29.4 (0.6)	28.2 (0.3)	0.05	28.2 (0.4)	27.1 (0.1)	0.03
Glycated Hemoglobin (%)	5.6 (0.03)	7.4 (0.3)	6.1 (0.1)	<0.001	6.1 (0.1)	5.4 (0.02)	<0.001
Fasting Total Cholesterol (mg/dL)	217.8 (0.9)	221.8 (4.4)	227.6 (2.0)	0.1	221.3 (4.5)	215.6 (0.9)	0.07
Use of ACEi/ARB	535 (6.0%)	46 (17.9%)	171 (13.3%)	0.2	24 (7.2%)	294 (4.5%)	0.09

Note: Values for categorical variables are given as number (weighted percentage); values for continuous variables, as weighted mean ± standard error. Conversion factor for total cholesterol in mg/dL to mmol/L, ×0.02586.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ACR, albumin-creatinine ratio; NHANES III, Third National Health and Nutrition Examination Survey.

* Includes history of myocardial infarction, heart failure or stroke.

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Table 2

Cox Proportional Hazards Models for All-Cause and Cardiovascular Mortality

	No. of Events	Weighted Mortality Rate[#]	Model 1[*]	Model 2[**]	P for Interaction[†]
All-Cause Mortality					
Retinopathy and CKD status					0.04
Neither retinopathy nor CKD	1519	14.5	1.00 (reference)	1.00 (reference)	
Retinopathy only	89	19.1	1.13 (0.84, 1.51)	1.02 (0.75, 1.38)	
CKD only	865	52.3	1.73 (1.54, 1.96)	1.52 (1.35, 1.72)	
Both CKD and retinopathy	161	69.2	3.22 (2.36, 4.40)	2.39 (1.77, 3.22)	
Retinopathy and eGFR status					0.6
Neither retinopathy nor low eGFR	1884	16.1	1.00 (reference)	1.00 (reference)	
Retinopathy only	173	25.9	1.32 (1.07, 1.64)	1.21 (0.96, 1.53)	
Low eGFR only	500	77.6	1.41 (1.19, 1.67)	1.39 (1.17, 1.65)	
Both retinopathy and low eGFR	77	93.2	2.15 (1.41, 3.27)	1.92 (1.27, 2.89)	
Retinopathy and albuminuria status					0.009
Neither retinopathy nor albuminuria	1858	16.5	1.00 (reference)	1.00 (reference)	
Retinopathy only	118	23.7	1.22 (0.93, 1.61)	1.07 (0.80, 1.44)	
Albuminuria only	526	46.1	1.83 (1.58, 2.11)	1.47 (1.30, 1.67)	
Both retinopathy and albuminuria	132	71.3	3.78 (2.82, 5.07)	2.65 (1.93, 3.64)	
Cardiovascular Mortality					
Retinopathy and CKD status					0.06
Neither retinopathy nor CKD	610	5.5	1.00 (reference)	1.00 (reference)	
Retinopathy only	30	7.4	1.11 (0.60, 2.05)	0.96 (0.50, 1.84)	
CKD only	439	26.4	2.05 (1.16, 2.39)	1.72 (1.47, 2.00)	
Both CKD and retinopathy	86	35.9	4.08 (2.83, 5.87)	2.96 (2.11, 4.15)	
Retinopathy and eGFR status					0.4
Neither retinopathy nor low eGFR	770	6.3	1.00 (reference)	1.00 (reference)	
Retinopathy only	67	10.5	1.33 (0.88, 2.02)	1.21 (0.77, 1.89)	
Low eGFR only	279	42.8	1.71 (1.34, 2.17)	1.61 (1.27, 2.03)	

	No. of Events	Weighted Mortality Rate[#]	Model 1[*]	Model 2[**]	P for Interaction[†]
Both retinopathy and low eGFR	49	55.8	2.88 (1.83, 4.54)	2.52 (1.60, 3.98)	
Retinopathy and albuminuria status					0.04
Neither retinopathy nor albuminuria	796	6.8	1.00 (reference)	1.00 (reference)	
Retinopathy only	46	9.7	1.16 (0.62, 2.17)	0.99 (0.50, 1.94)	
Albuminuria only	253	21.4	1.84 (1.53, 2.22)	1.41 (1.20, 1.67)	
Both retinopathy and albuminuria	70	38.2	4.54 (3.23, 6.36)	3.16 (2.28, 4.37)	

Note: Unless otherwise indicated, values are given as hazard ratio (95% confidence interval).

[#]Weighted mortality rates per 1000 person-years.

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

[*]Model 1: Adjusted for age, gender, race/ethnicity, education and annual family income

[**]Model 2: Adjusted for variables in model 1 plus smoking status, hypertension, hemoglobin A1C, diabetes, cardiovascular disease, family history of coronary heart disease, body mass index, and total cholesterol. In addition, analyses of microalbuminuria and retinopathy were adjusted for eGFR; and analyse of eGFR and retinopathy were adjusted for natural log of urine ACR.

[†]Interaction between retinopathy and either CKD, low eGFR or microalbuminuria