Prevalence of Diabetic Retinopathy and Associated Mortality Among Diabetic Adults With and Without Chronic Kidney Disease

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• PURPOSE: To estimate prevalence and severity of diabetic retinopathy (DR) among U.S. adults with diabetes and with or without chronic kidney disease (CKD), and assess associated risk of mortality.

• DESIGN: Cross-sectional study with national survey data.

• METHODS: The cohort included adults ≥40 years old with diabetes in the National Health and Nutrition Examination Surveys (NHANES) 2005–2008. Vital status was determined through December 31, 2011. We defined diabetes as hemoglobin A1c ≥6.5% or self-report and CKD by urinary albumin/creatinine ≥30 mg/g or glomerular filtration rate < 60 mL/min/1.73 m^2. The main outcomes were DR and mortality.

• RESULTS: Prevalence of DR was 27.8% (95% CI 24.3–31.7), 36.2% (95%CI 30.1–42.7), and 23.4% (95% CI 19.2–28.1), overall, with and without CKD. Prevalence of vision-threatening DR was 4.2% (95% CI 3.2–5.5), 8.2% (95% CI 5.4–12.2), and 2.0% (95% CI 1.2–3.5), respectively. In a multivariable adjusted model, DR was positively but nonsignificantly associated with CKD (OR = 1.1, 95% CI 0.7–1.7), was 40% higher per 1% increase in hemoglobin A1c (OR = 1.4, 95% CI 1.1–1.6), was 30% higher per 5 years additional diabetes duration (OR = 1.3, 95% CI 1.1–1.5), was 30% higher per 10 mm Hg increase in systolic blood pressure (OR = 1.3, 95% CI 1.1–1.5), and was 6-fold higher with insulin treatment (OR = 6.2, 95% CI 2.6–14.8). Compared with diabetic participants with neither DR nor CKD, those with DR and CKD had a 3.6-fold (95% CI 1.5–9.1) increased adjusted risk for all-cause mortality.

• CONCLUSIONS: Over one third of persons with diabetes and CKD had DR. The risk of death was higher with than without CKD and DR. Many of the studied risk factors associated with DR are modifiable. (Am J Ophthalmol 2019;198:200–208. Published by Elsevier Inc.)

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BOTH CHRONIC KIDNEY DISEASE (CKD) AND DIABETIC retinopathy (DR) are frequent microvascular complications of longstanding diabetes. In the United States, 40% of adults with diabetes have CKD, which often leads to cardiovascular complications and kidney failure.[1] DR affects nearly one third of adults with diabetes, and represents the leading cause of blindness in these people.[2,3] In addition to severely influencing the long-term consequences of diabetes, the coexistence of these microvascular complications may be an important indicator of disease severity and risk of CKD progression to end-stage renal disease.[4] In people with type 2 diabetes, CKD can be caused by several factors other than diabetes, but is known to be more likely to progress to kidney failure when it is attributable to diabetes.[5] Specifically, the presence of DR in persons with severe albuminuria is strongly suggestive of diabetic kidney disease, whereas the absence of DR in persons with normal or moderate albuminuria and glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 suggests nondiabetic causes of CKD, such as hypertension, renal artery stenosis, or systemic diseases.[6–8] Screening for DR may therefore additionally inform on the necessity for further investigation into the etiology of kidney disease and on the severity of diabetes-related CKD, and present an opportunity to prevent progression to kidney failure.

Population-based estimates of the prevalence and severity of DR are unknown among people with both diabetes and CKD. In addition, DR has been associated with increased risk of all-cause and cardiovascular mortality in populations with diabetes and CKD, whereas the relationship is less clear in diabetes populations without CKD.[9]

The aim of this study is to estimate the prevalence of DR and vision-threatening DR (VTDR) among adults ≥40 years old with diabetes, and with or without CKD participating in the National Health and Nutrition Examination Surveys (NHANES) 2005–2008 and to assess the associations between these microvascular complications of diabetes and mortality.

METHODS

• STUDY POPULATION: We used 2005–2008 NHANES data for this analysis. The NHANES is a cross-sectional survey of the health and nutritional status of the U.S.

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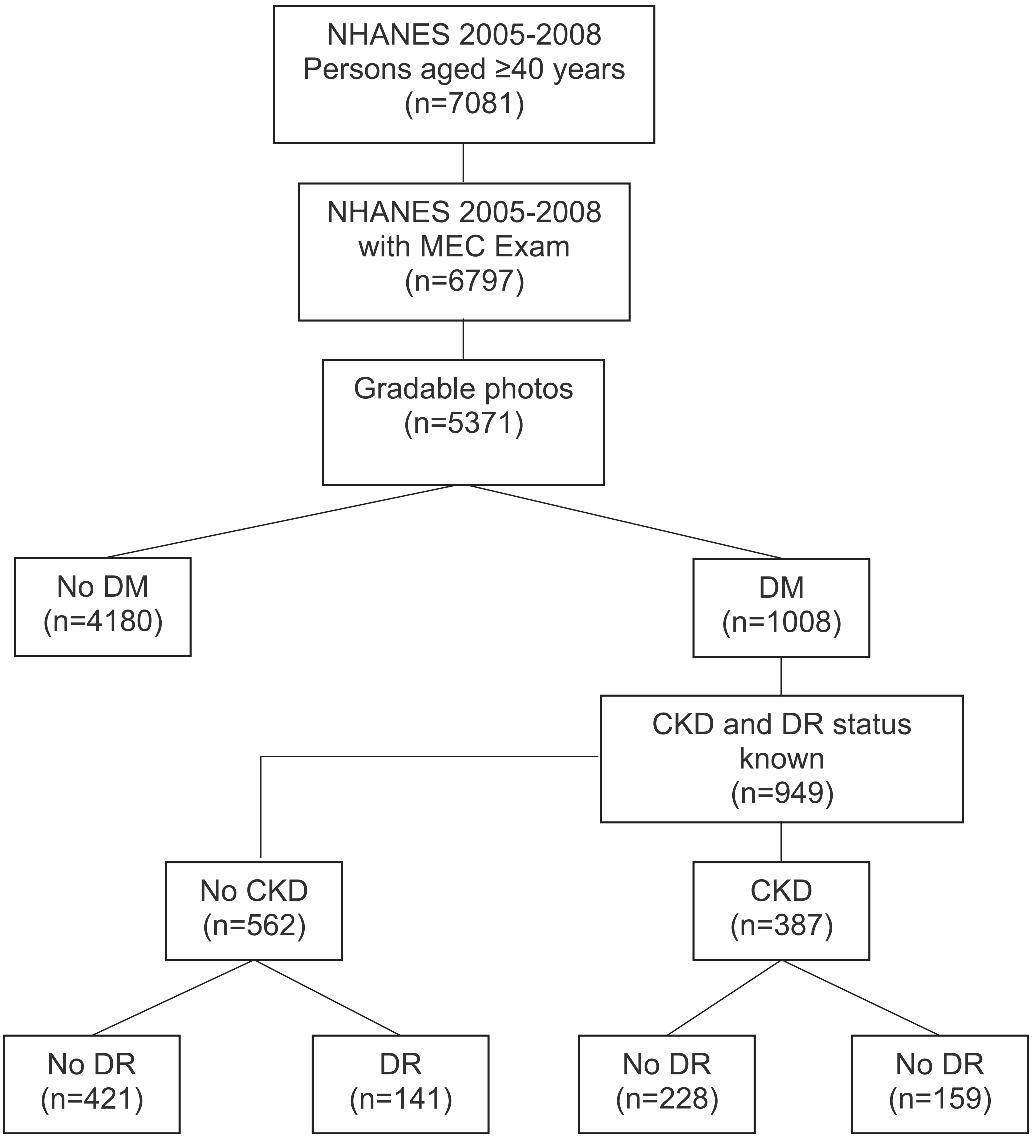

FIGURE 1. Cohort selection flowchart for National Health and Nutrition Examination Surveys (NHANES) 2005–2008. CKD = chronic kidney disease; DM = diabetes mellitus; DR = diabetic retinopathy; MEC = mobile examination center.

civilian, noninstitutionalized population conducted by the National Center of Health Statistics (NCHS), Centers for Disease Control and Prevention.[10] Participants are randomly selected through a complex, multistage cluster sampling probability design. NHANES collects data through interviews in participants' homes and conducts medical examinations and laboratory assessments in a mobile examination center (MEC). Additional information on NHANES is available at http://www.cdc.gov/nchs/nhanes.htm. The primary analyses in this report use combined data from 2 survey periods, 2005–2006 and 2007–2008, and included participants 40 years and older because assessment of retinal diseases was performed in this age range only. Of the 7081 participants aged ≥40 years in NHANES 2005–2008, 6797 (96%) reported to the MEC for a health examination (Figure 1). All these participants were eligible for the eye examination except those who were blind (had no light perception); had an eye infection; or wore eye patches on both eyes. Among the participants who had the MEC examination, 5894 (87%) received the retinal imaging and among those, 5371 (91%) had complete gradable photographs for either right or left eye.

• **LABORATORY MEASURES:** Hemoglobin A1c assays were performed on whole blood using high-pressure liquid chromatography (coefficients of variation <3.0%).[10] Urinary and serum creatinine were measured by the Jaffé kinetic alkaline picrate method performed on a Roche Hitachi 917 analyzer (Hitachi [Roche/Hitachi Cobas 6000 Analyzer. Roche Diagnostics, Indianapolis, IN, USA]) and a Beckman Synchron LX20 analyzer (Beckman Instruments, Inc. [Brea, CA, USA: Beckman Instruments, Inc]).

All serum creatinine measurements are calibrated according to the Information Display Measurements Standard (IDMS).[10] Urinary albumin was measured by solid-phase fluorescent immunoassay. Urinary albumin excretion was estimated by computing the albumin-to-creatinine ratio (ACR) in units of mg/g. ACR was considered normal if <30 mg/g and elevated if ≥30 mg/g. Estimated glomerular filtration rate (eGFR) was computed using the CKD-EPI equation.[11] CKD was defined by the presence of elevated albuminuria or an eGFR <60 mL/min/1.73 m^2. CKD stages 1–2 are defined by albuminuria and eGFR ≥60 mL/min/1.73 m^2; CKD stages 3–5 are defined by eGFR <60 mL/min/1.73 m^2 regardless of albuminuria.[12]

Diabetes was defined by self-report of diagnosis by a doctor or other health professional or A1c ≥6.5%. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or self-report of diagnosis by a doctor or other health professional. Body mass index (BMI) was defined as weight divided by the square of height (kg/m^2). Environmental exposure to tobacco was assessed by serum cotinine levels and classified as follows: no exposure (limit of detection to <1 ng/mL), passive exposure or light smoker (1–9 ng/mL), and heavy smoker (≥10 ng/mL).

• **OCULAR CONDITION MEASURES:** In 2005–2008, the Canon CR6-45NM ophthalmic digital imaging system and Canon EOS 10D digital camera (Canon, Tokyo, Japan) was used to take 2 images per eye of both eyes. One image was centered on the macula and the second on the optic nerve. The digital images were graded by masked graders at the University of Wisconsin Ocular Epidemiologic Reading Center, Madison, using a modification of the Airlie House classification system.[13,14] Details of capture and grading of digital images and quality control have been described previously.[15]

DR was defined by the presence of ≥1 retinal microaneurysm or retinal blot hemorrhage with or without more severe lesions (hard exudates, soft exudates, intraretinal microvascular abnormalities, venous beading, retinal new vessels, preretinal and vitreous hemorrhage, and fibroproliferans) using the Early Treatment Diabetic Retinopathy Study (ETDRS) grading standards.[16] VTDR, a level of DR that may soon result in vision loss if left untreated, was defined by the presence of severe nonproliferative DR, proliferative DR, or clinically significant macular edema. Clinically significant macular edema was considered present when edema involved the fovea or was within 500 μm of the fovea, or when a 1+ disc area of edema was present with at least a portion of it within the macula.

• **VITAL STATUS:** The vital status of the cohort was determined from the NHANES 2005–2006 and 2007–2008 public-use linked mortality files. The linked files provide vital status and follow-up in person-months from the date of NHANES survey participation through the date of death or December 31, 2011. Mortality was ascertained by NCHS through a probabilistic match between NHANES 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. Cause-of-death coding was assigned by NCHS based on the 10th revision of the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD-10). Among the codes included were I00-I09, I11, I13, I20-I51 for diseases of the heart; C00-C97 for malignancy; I60-I69 for cerebrovascular diseases; and E10-E14 for diabetes (https://www.cdc.gov/nchs/data/datalinkage/Public_use_Data_Dictionary_23_2015.pdf).

• **STATISTICAL METHODS:** We present clinical and demographic characteristics as means or percentages, with 95% confidence intervals (CIs) overall, and by CKD and DR. The estimated prevalence of DR and VTDR is presented among persons with and without diabetes-related CKD. We explored the demographic and clinical determinants of DR using logistic regression models, and examined the adequacy of the fit of the final model by the log-likelihood ratio. Cox regression models (proc survival) were used to evaluate the association of DR and CKD with all-cause mortality. Each model included a categorical variable (unadjusted and adjusted) that represented the 4 combinations of CKD (0/1) and DR (0/1); those with absent CKD (0) and absent DR (0) represented the reference category. Data were analyzed using sample weights to account for differential probabilities of sample selection, nonresponse, and sample noncoverage.

To explore changes over time in a secondary analysis, the prevalence of DR and VTDR in persons with both diabetes and CKD was compared in NHANES 2005–2008 and NHANES 1988–1994. In the earlier cohort, a nonstereoscopic, color, 45-degree photograph, centered between the optic nerve and the macula, was taken of 1 randomly selected eye. The camera used was a Canon CR4-45NM "nonmydriatic" fundus camera, which incorporated the use of an infrared video camera to allow photographs to be taken in a darkened examination room without the use of dilating drops. Prevalence of DR and VTDR for a random 1 eye (the right eye if the last digit of the participant identification number was even and the left eye if it was odd) in NHANES 2005–2008 was explored relative to NHANES 1988–1994 using logistic regression models adjusted for age, sex, race/ethnicity, blood pressure, and hemoglobin A1c.

We used SAS 9.3 for Windows software (SAS Institute, Cary, North Carolina, USA) for data management and SUDAAN 11 software (Research Triangle Institute, Research Triangle Park, North Carolina, USA) to obtain point estimates and 95% CI, using the Taylor series linearization method to account for the survey design. We considered statistical significance at a *P* value of .05 or less.

TABLE 1. Characteristics of the National Health and Nutrition Examination Surveys 2005–2008 Participants Aged 40 Years and Older With Diabetes, and by Chronic Kidney Disease and Diabetic Retinopathy Status

		No CKD		CKD	
	All With Diabetes (N = 949)	Without DR (N = 421)	With DR (N = 141)	Without DR (N = 228)	With DR (N = 159)
Age, years	60.4 (59.5–61.4)	58.3 (57.2–59.5)	58.1 (56.0–60.2)	63.6 (62.1–65.2)	65.9 (64.3–67.5)[c]
Diabetes duration, years	9.9 (9.1–10.6)	6.8 (5.9–7.8)	12.2 (10.7–13.8)[c]	8.4 (6.9–10.0)	18.3 (15.1–21.6)[c]
Hemoglobin A1c, %	7.2 (7.1–7.4)	7.0 (6.8–7.2)	7.9 (7.6–8.3)[c]	7.0 (6.7–7.2)	7.7 (7.4–8.0)[c]
LDL cholesterol, mg/dL	103.2 (98.2–108.1)	101.5 (95.3–107.6)	111.2 (100.3–122.2)	106 (95.6–116.4)	94.3 (82.6–105.9)
HDL cholesterol, mg/dL	47.4 (46.2–48.6)	46.4 (44.7–48.0)	48.5 (46.3–50.7)	47.8 (43.9–51.7)	49.7 (46.8–52.7)
Triglycerides, mg/dL	184.0 (164.2–203.8)	187.4 (144.0–230.8)	157.7 (122.0–193.4)	197.3 (162.7–231.9)	183.5 (139.0–228.1)
Serum uric acid, mg/dL	5.8 (5.6–5.9)	5.6 (5.5–5.8)	5.3 (5.0–5.6)[c]	6.1 (5.8–6.4)	6.3 (5.8–6.7)
ACR, mg/g[a]	12.3 (6.7–31.7)	8.9 (5.5–14.3)	9.3 (6.2–17.4)	45 (30–90)	68 (23–423)
eGFR, mL/min/1.73 m^2	82.4 (80.7–84.2)	88.9 (86.6–91.2)	91.3 (87.6–94.9)	72 (68–76)	65 (59–70)
Systolic BP, mm Hg	131 (129–133)	129 (126–131)	128 (123–133)	133 (129–138)	142 (136–147)[c]
Diastolic BP, mm Hg	70 (69–71)	71 (69–73)	69 (67–72)	71 (68–74)	63 (60–67)[c]
Percent (95% CI)					
Female	50.3 (45.5–55.0)	53.2 (46.5–59.8)	37.2 (29.5–45.6)[c]	51.4 (39.1–63.6)	52.3 (42.5–61.9)
Race/ethnicity					
Non-Hispanic white	65.4 (56.5–73.4)	66.7 (56.2–75.9)	59.5 (45.3–72.2)	68.5 (57.3–77.8)	62.1 (52.1–71.2)
Non-Hispanic black	16.6 (12.3–21.9)	14.0 (9.4–20.3)	22.8 (15.4–32.3)	14.5 (9.5–21.5)	23.0 (16.8–30.7)
Hispanic	13.1 (9.5–17.8)	12.1 (8.2–17.6)	16.0 (9.3–26.0)	12.7 (7.7–20.3)	14.2 (7.9–24.2)
Others	4.9 (2.8–8.5)	7.2 (3.8–13.3)	1.8 (0.4–8.2)	4.3 (1.7–10.7)	0.6 (0.2–2.8)
Type 1 diabetes	1.3 (0.5–3.0)	0.2 (0.03–1.6)	5.3 (1.6–16.5)	0	2.8 (0.8–9.2)
Insurance coverage	88.4 (85.3–90.9)	88.1 (83.2–91.8)	82.0 (72.4–88.8)	92.8 (88.5–95.6)	89.7 (83.9–93.6)
Education					
High school	57.6 (52.3–62.8)	49.6 (42.2–57.1)	57.0 (46.5–66.9)	72.9 (62.4–81.4)	63.0 (54.2–70.9)
More than high school	42.4 (37.3–47.7)	50.4 (42.9–57.9)	43.0 (33.1–53.5)	27.1 (18.6–37.6)	37.0 (29.1–45.8)
Hypoglycemic treatment					
Oral agents	48.6 (43.6–53.7)	49.4 (42.45–56.4)	43.8 (35.1–52.9)	54.7 (45.5–63.6)	40.4 (32.6–48.7)
Insulin	20.0 (17.0–23.5)	8.9 (6.1–12.7)	39.2 (29.9–49.3)[c]	13.3 (9.4–18.5)	53.0 (44.5–61.4)[c]
Albuminuria[b]	25.5 (22.5–28.9)			75.3 (67.7–81.6)	73.1 (64.0–80.6)
eGFR <60 mL/min/1.73 m^2	15.7 (13.3–18.3)			40.9 (32.6–49.8)	52.4 (44.0–60.7)
CKD	34.8 (31.3–38.4)	0	0	100.0	100.0
DR	27.8 (24.3–31.7)	23.4 (19.2–28.1)		36.2 (30.1–42.7)	
VTDR	4.2 (3.2–5.5)	2.0 (1.2–3.5)		8.2 (5.4–12.4)	
BMI, kg/m^2					
25–30	26.4 (22.4–30.8)	23.9 (19.5–28.9)	32.0 (20.9–45.5)	24.6 (18.5–31.9)	32.7 (22.7–44.7)
≥30	62.7 (58.3–66.9)	65.6 (60.3–70.5)	55.3 (43.6–66.5)	63.8 (54.8–72.0)	58.5 (47.7–68.5)
Hypertension	74.3 (70.9–77.4)	67.6 (61.1–73.5)	68.7 (57.9–77.8)	84.8 (77.6–90.0)	88.7 (79.3–94.1)
Serum cotinine levels					
1–9 ng/mL	4.2 (2.9–6.0)	4.2 (2.2–7.7)	6.1 (2.7–13.3)	3.5 (1.8–6.8)	3.0 (1.9–4.7)
≥10 ng/mL	21.8 (17.9–26.2)	21.8 (16.8–27.7)	13.7 (8.8–20.7)	25.6 (19.1–33.5)	24.5 (17.1–33.9)
History of CVD	26.8 (22.9–31.2)	17.3 (13.2–22.3)	25.9 (19.0–34.2)[c]	41.3 (31.5–51.8)	40.2 (31.2–49.9)
ACEi or ARB treatment	51.4 (46.6–56.1)	43.7 (35.8–51.9)	48.9 (37.7–60.3)	63.6 (56.5–70.2)	63.2 (52.4–72.8)

A1c = hemoglobin A1c; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; CKD = chronic kidney disease; CVD = cardiovascular disease; DBP = diastolic blood pressure; DR = diabetic retinopathy; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SBP = systolic blood pressure; VTDR = vision-threatening diabetic retinopathy.

Results are mean (95% CI) or percent (95% CI) unless otherwise indicated.

[a]Values represent median, 25th and 75th percentiles.

[b]Defined as ACR ≥30 mg/g.

[c]$P < .05$ compared with no DR.

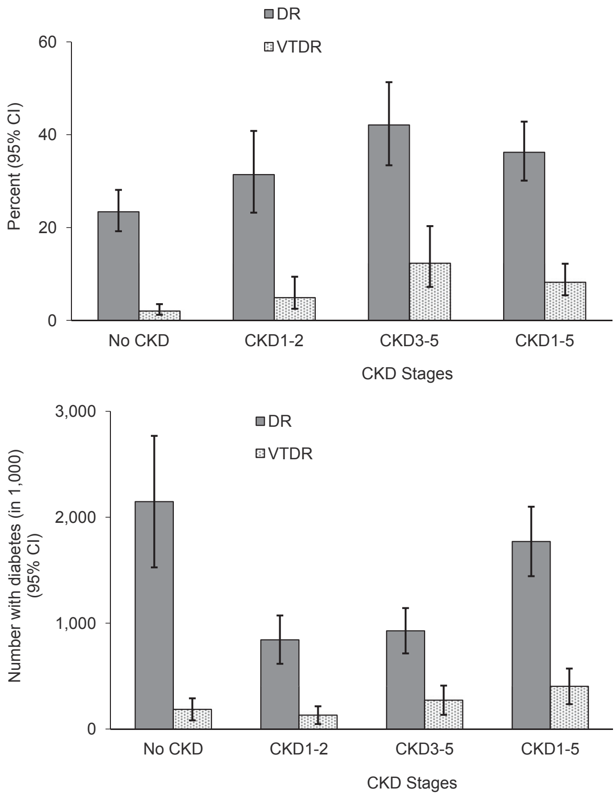

FIGURE 2. Prevalence (Top) and absolute numbers (Bottom) (and 95% confidence interval) of diabetic retinopathy (DR) and of vision-threatening diabetic retinopathy (VTDR), by chronic kidney disease (CKD) and CKD stages, in adults ≥40 years old with diabetes in National Health and Nutrition Examination Surveys (NHANES) 2005–2008.

RESULTS

IN NHANES 2005–2008, THERE WERE 949 PARTICIPANTS ≥40 years old with diabetes and information on CKD and DR status. These were generally older, with higher A1c and higher prevalence of hypertension, hypoglycemic and RAS treatments, and obesity, compared with those who had no information on the 2 microvascular complications (n = 242) (Supplemental Table 1; Supplemental Material at AJO.com). Among those included in the study, 387 (34.8%) had CKD (representing 4.9 million adults nationally) and 300 (27.8%) had DR (representing 3.9 million adults). Among those with CKD, 159 (36.2%, 95% CI 30.1–42.7) also had DR (representing 1.8 million adults) and 37 (8.2%, 95% CI 5.4–12.2) had VTDR (representing 0.4 million adults). Demographic and clinical characteristics of participants with diabetes overall, and by CKD and DR status, are shown in Table 1. Regardless of the presence of CKD, persons with DR had longer duration of diabetes, had higher hemoglobin A1c, and were more likely to be treated with insulin than with oral antidiabetic agents compared with those without DR. In addition, persons with DR and without CKD had higher serum uric acid level and were more likely to be male and to report a history of CVD; those with DR and CKD were also older and with higher blood pressure than those without DR. Treatment with renin-angiotensin system inhibitors (ACEi or ARB) was reported more frequently among participants with CKD and did not differ by DR status.

Prevalence estimates of DR and VTDR were higher with higher CKD stages. The prevalence of DR was 23.4% (95% CI 19.2–28.1), 31.4% (95% CI 23.2–40.8), and 42.1% (95% CI 33.4–51.3) in those without CKD, CKD stages 1–2, and CKD stages 3–5, respectively (Table 1 and Figure 2, Top). For VTDR, prevalence estimates were 2.0% (95% CI 1.2–3.5), 4.9% (95% CI 2.5–9.4), and 12.3% (95% CI 7.2–20.3) in those without CKD, CKD stages 1–2, and CKD stages 3–5, respectively. In absolute numbers, there were fewer people with than without CKD and therefore the highest number of persons with DR falls in the category of no CKD (Figure 2, Bottom).

The unadjusted and demographically adjusted odds of DR among people with diabetes were nearly twice as high in the presence of CKD; however, further adjustments rendered this association nonsignificant (OR = 1.1, 95% CI 0.7–1.7, $P = .79$) (Table 2). In the fully adjusted model the odds of DR were twice as high in men than in women (2.1, 95% CI 1.4–3.2), 40% higher per 1% increase in hemoglobin A1c (95% CI 1.1–1.6), 30% higher for every additional 5 years diabetes duration (95% CI 1.1–1.5), 30% higher per 10 mm Hg increase in systolic blood pressure (95% CI 1.1–1.5), and 6-fold higher in participants on insulin treatment compared with those who were not on antihyperglycemic treatment (OR = 6.2, 95% CI 2.6–14.8) ($P < .001$ for each risk factor) (Table 2). Interaction terms between each covariate and CKD status in the fully adjusted model were nonsignificant, suggesting that these risk factors contribute similarly to DR in persons with or without CKD.

During a median follow-up of 4.5 years (interquartile range 3.4–5.5 years), 110 deaths occurred among the 949 participants with diabetes. The leading causes of death were malignancy (n = 22), heart disease (n = 20), diabetes (n = 11), and cerebrovascular disease (n = 7). The age-, sex-, and race/ethnicity-adjusted risk of death was positively but nonsignificantly associated with DR only (HR = 1.4, 95% CI 0.5–4.0) and with CKD only (HR = 1.9, 95% CI 0.8–4.4), and significantly 3.6-fold higher in those with both DR and CKD (HR = 3.6, 95% CI 1.5–9.1, $P = .01$) compared with participants with neither CKD nor DR (reference group death rate = 11.9 per 1000 person-years, 95% CI 3.1–20.9) (Table 3). Additional adjustments for A1c and systolic blood pressure lowered the point estimates for the associations but not the level of significance. These associations remained with additional inclusion of serum cotinine level, hypoglycemic treatment, and history of cardiovascular disease in the model, although with wider confidence limits.

TABLE 2. Multiple Logistic Regression for Diabetic Retinopathy in Participants Aged 40 Years and Older With Diabetes, National Health and Nutrition Examination Surveys 2005–2008

	Odds Ratio (95% CI)		
Covariates	Unadjusted	Model 1	Model 2
CKD (yes vs no)	1.9 (1.3–2.6)	1.7 (1.2–2.4)	1.1 (0.7–1.7)
Age (per 5 years)		1.1 (0.99–1.14)	1.0 (0.8–1.1)
Sex			
Female		1 [Reference]	1 [Reference]
Male		1.5 (1.1–2.0)	2.1 (1.4–3.2)
Race/ethnicity			
Non-Hispanic white		1 [Reference]	1 [Reference]
Non-Hispanic black		2.0 (1.2–3.1)	1.8 (1.0–3.5)
Hispanic		1.5 (0.9–2.5)	1.6 (0.8–3.0)
Others		0.3 (0.1–1.2)	0.6 (0.1–3.0)
SBP (per 10 mm Hg)			1.3 (1.1–1.5)
DBP (per 10 mm Hg)			0.7 (0.6–0.9)
Exposure to tobacco[a]			
No exposure			1 [Reference]
Passive exposure or light smoker			2.5 (0.8–8.4)
Heavy smoker			1.1 (0.6–2.2)
Hemoglobin A1c (per 1%)			1.4 (1.1–1.6)
Diabetes duration (per 5 years)			1.3 (1.1–1.5)
Hypoglycemic treatment			
No treatment			1 [Reference]
Oral agents only			1.7 (0.7–4.1)
Insulin			6.2 (2.6–14.8)

CKD = chronic kidney disease; DBP = diastolic blood pressure; DR = diabetic retinopathy; SBP = systolic blood pressure.

[a]Defined by serum cotinine levels as follows: no exposure (limit of detection to < 1 ng/mL), passive exposure or light smoker (1–9 ng/mL), and heavy smoker (≥10 ng/mL). DR is the dependent variable; covariates are independent variables in the models, as indicated in the table.

TABLE 3. Unadjusted and Adjusted Hazard Ratio (95% Confidence Interval) of All-Cause Mortality, by the Presence of Chronic Kidney Disease and Diabetic Retinopathy

Participants With Diabetes	Deaths/No. in Category	Unadjusted HR (95% CI)	Model 1 (95% CI)	*P*	Model 2 (95% CI)	*P*
No CKD, no DR	22/421	1 [Reference]	1 [Reference]		1 [Reference]	
DR, no CKD	12/141	1.4 (0.5–4.3)	1.4 (0.5–4.0)	.51	1.1 (0.3–3.6)	.9
CKD, no DR	37/228	2.7 (1.2–6.4)	1.9 (0.8–4.4)	.14	1.4 (0.6–3.3)	.5
CKD and DR	39/159	5.7 (2.4–13.6)	3.6 (1.5–9.1)	.01	3.0 (1.03–8.8)	.04

CKD = chronic kidney disease; DR = diabetic retinopathy; HR = hazard ratio.

Model 1 is adjusting for age (per 5 years), sex, and race/ethnicity. Model 2 is additionally adjusting for hemoglobin A1c (per 1%) and systolic blood pressure (per 10 mm Hg). Each model includes the 4 CKD and DR status categories.

When examining changes over time using random single-eye measurements, the prevalence of DR among persons with CKD was 30.7% (95% CI 25.5–36.4) and of VTDR 6.1% (95% CI 3.8–9.7) for NHANES 2005–2008; this compared to 24.0% (95% CI 18.0–31.3) and 2.6% (95% CI 1.2–5.2), respectively, for NHANES 1988–1994. The prevalence of DR was significantly higher in the more recent survey years than in the earlier NHANES after adjusting for age, sex, race/ethnicity, mean arterial blood pressure, and hemoglobin A1c, whereas the change in prevalence estimate of VTDR was not significant, likely owing to the small number of cases (Table 4).

DISCUSSION

IN A REPRESENTATIVE SAMPLE OF THE UNITED STATES POPulation aged 40 years and older with diabetes, nearly one third had DR and this percentage was higher in those

TABLE 4. Change in Prevalence of Diabetic Retinopathy and Vision-Threatening Diabetic Retinopathy in Persons With Both Diabetes and Chronic Kidney Disease Aged 40 Years and Older, Between 1988–1994 and 2005–2008 National Health and Nutrition Examination Surveys[a]

NHANES Period	Unadjusted Prevalence (95% CI)	Prevalence Ratio (95% CI)	*P*	Adjustment
DR				
1988–1994	24.0 (18.0–31.3)	1 [Reference]		
2005–2008	30.7 (25.5–36.4)	1.3 (0.9–1.8)	.13	Unadjusted
		1.3 (0.9–1.8)	.19	Age, sex, race/ethnicity
		1.5 (1.1–2.1)	.02	+ MAP, A1c
VTDR				
1988–1994	2.6 (1.2–5.2)	1 [Reference]		
2005–2008	6.1 (3.8–9.7)	2.3 (1.00–5.6)	.048	Unadjusted
		2.1 (0.9–5.1)	.09	Age, sex, race/ethnicity
		2.9 (0.98–8.6)	.05	+ MAP, A1c

A1c = hemoglobin A1c; DR = diabetic retinopathy; MAP = mean arterial blood pressure; NHANES = National Health and Nutrition Examination Survey; VTDR = vision-threatening diabetic retinopathy.
[a]Prevalence estimates are based on 1 eye only in NHANES 1988–1994 and on a random 1 eye in NHANES 2005–2008.

with than without CKD. Among those with CKD, 1.8 million people had DR and 0.4 million had VTDR, indicating an important segment of the population with diabetes at high risk for CKD progression and blindness.[17] Among persons with diabetes in general, the odds of having DR were positively associated with duration of diabetes and more severe disease (ie, those on insulin treatment), systolic blood pressure, A1c, and male sex. These risk factors contributed similarly to DR in persons with or without CKD. Participants with CKD and DR were 3.6 times more likely to die during follow-up than those with neither CKD nor DR, mainly of malignancy and cardiovascular disease. Because the survey design does not differentiate the type of diabetes, the present results largely reflect the experience of noninstitutionalized persons with type 2 diabetes in the United States.

Longitudinal and cross-sectional studies in several populations with type 2 diabetes reported associations between CKD and DR, using various definitions for these complications (Supplemental Table 2; Supplemental Material at AJO.com). The risk of DR in previous studies was 2- to 3-fold higher in the presence of CKD, with a higher risk generally described for more advanced stages of CKD.[17–19] In the Chronic Renal Insufficiency Cohort, a longitudinal multicenter study of adults with eGFR <60 mL/min/1.73 m^2 (CKD stage 3) in the United States,[20] worse ETDRS retinopathy scores were significantly and independently associated with lower kidney function among those with diabetes. Other studies in people with type 1 or type 2 diabetes have reported a bidirectional relationship between CKD and DR,[21,22] supporting the common pathology underlying microvascular complications of diabetes. It also suggests that a positive diagnostic for one of these complications should prompt a recommendation for evaluation of the other.

The presence of DR is a useful guide for identifying persons most likely to have CKD owing to diabetic glomerulopathy, while its absence among persons with diabetes appears to be predictive of nondiabetic nephropathy.[23–25] Meta-analyses of studies including clinical and research kidney biopsies in persons with type 2 diabetes identified the absence of DR, shorter duration of diabetes, and lower A1c as significant predictors of nondiabetic nephropathy.[23,26] This differentiation has important clinical implications, as it may redirect treatment decisions toward specific etiologies of CKD. In addition, people with diabetic nephropathy have a worse renal and overall survival compared with those with nondiabetic or mixed forms of kidney disease, particularly when presenting with acute kidney injury.[25] Together, these observations indicate that retinal examination, a simple and noninvasive ambulatory test, may provide additional insight when screening people with diabetes for kidney biopsy, inform on the necessity for further investigation into the etiology of kidney disease and on the severity of diabetes-related CKD, and present an opportunity to prevent progression to kidney failure.

In the present study the occurrence of either CKD or DR related positively with risk of death; however, this association was significant in participants with both CKD and DR only, with a 3-fold higher risk of all-cause mortality than among those with neither of these microvascular complications. These results concur with a previous study in a nationally representative U.S. cohort with diabetes, which found a 2.5-fold higher overall death rate among those with than without CKD and DR during a median of 14.5 years of follow-up.[9] Different from the present results, this prior study found an inverse association between retinopathy and mortality in individuals without CKD. This inconsistency may be attributed, at least in part, to different definitions of diabetes and ascertainment of retinopathy. Even so, CKD and DR share the same risk factors and treating these common risk factors, including hyperglycemia, high blood pressure, and high cholesterol, among people with diabetes is known to delay the onset and progression of CKD[27] and may have a similar effect on DR.[28]

Among participants with both diabetes and CKD in the NHANES, prevalence of DR was 50% higher in 2005–2008 than in 1988–1994 and prevalence of VTDR nearly 3-fold higher, although the adjusted difference was significant for overall DR only. This observation is consistent with a previous study among NHANES participants with diabetes.[2] The higher estimates may represent true increases in DR prevalence, but may also reflect improved case finding with digital imaging in the recent cohort, or with better CKD diagnosis after 2002, when definition and staging of CKD were introduced and widely adopted.[12] Of note, studies of agreement indicate no significant systematic difference between gradings from film and digital images,[29] suggesting that overall bias owing to methodologic changes between the 2 NHANES cohorts is negligible.

The findings in this report are subject to some limitations. First, the cross-sectional design of NHANES does not allow a cause-and-effect assessment for the comorbidities of interest. Secondly, the level of albuminuria was measured in single random urine collections; therefore overall prevalence of participants with both diabetes and CKD may be overestimated. Third, the small sample sizes, especially of VTDR, might have prevented detection of differences, if they existed, between and among subgroups. Nonetheless, the strength of this study resides in the analysis of a nationally representative adult population with both diabetes and CKD. This study may also be limited in that it uses older (NHANES 2005–2008) observations. However, it is unlikely that relative associations between CKD and DR have changed in a 10-year time span. We therefore believe these data to be relevant to today's CKD population.

In conclusion, nearly one third of this nationally representative sample of adults with diabetes had DR. The prevalence of DR was higher among those with than without CKD, indicating that over one third of people with diabetes-related CKD, or 1.8 million, are at increased risk for progression to kidney failure. In addition, a significantly higher proportion of participants with than without CKD had VTDR, representing people at high risk for blindness. Both CKD and DR increase the risk for all-cause mortality. DR and CKD share many similar risk factors and most of these are modifiable. This observation suggests that a positive diagnostic of one of these microvascular complications should prompt a recommendation for evaluation of the other. Public health strategies targeting their common risk factors, and particularly type 2 diabetes prevention, may prevent the onset or progression of CKD and DR, with the greatest impact in those who are at highest risk.

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