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Original Contribution

Defining Incident Chronic Kidney Disease in the Research Setting

The ARIC Study

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Deaths of participants and losses to follow-up pose challenges for defining outcomes in epidemiologic studies. The authors compared several definitions of incident chronic kidney disease (CKD) in terms of incidence, agreement, and risk factor associations. They used data from 14,873 participants in the community-based, multicenter, biracial Atherosclerosis Risk in Communities Study (1987–1999). The estimated glomerular filtration rate (eGFR) was based on serum creatinine at baseline and the 3- and 9-year follow-up visits. Hospitalizations were ascertained continuously. The authors compared 4 definitions of incident CKD: 1) low eGFR ($<$60 mL/minute/1.73 m^2); 2) low and declining ($\geq$25%) eGFR; 3) an increase in serum creatinine ($\geq$0.4 mg/dL) at 3- or 9-year follow-ups; and 4) CKD-related hospitalization or death. From these definitions, they identified 1,086, 677, 457, and 163 cases, respectively. There was relatively good agreement among definitions 1–3, but definition 4 identified mostly different cases. Risk factor associations were consistent across definitions for hypertension and lipids. Diabetes showed weaker associations with definition 1 (incidence rate ratio = 1.5, 95% confidence interval: 1.2, 1.7) than with definition 4 (incidence rate ratio = 6.3, confidence interval: 4.4, 8.9). Associations with gender differed in direction and magnitude across definitions. Case definition can impact relative risk estimates for CKD risk factors.

cohort studies; diagnostic techniques and procedures; incidence; kidney diseases

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICD-9, *International Classification of Diseases,* Ninth Revision; ICD-10, *International Classification of Diseases,* Tenth Revision.

Editor's note: *An invited commentary on this article appears on page 425.*

National guidelines define and stage prevalent chronic kidney disease (CKD) for clinical practice on the basis of the presence of persistent albuminuria and/or a reduced glomerular filtration rate. However, there is no standard definition for incident CKD over time in the research setting.

Defining incidence is far more complicated than defining prevalent disease. In the former, longitudinal follow-up data and stable laboratory calibration of kidney disease markers are needed to detect changes over time. Collection of longitudinal data is often limited by losses to follow-up due to attrition, death, or illness precluding continued participation in study visits. Defining incident cases also becomes difficult when cases are defined by administration of medical care rather than by direct measures of disease, as access to and intensity of care influence these outcomes. There are no standards on how to combine such clinical outcomes with outcomes based on laboratory results (e.g., rise in serum creatinine). Large prospective studies have relied on serum creatinine and *International Classification of Diseases* codes to define CKD incidence, but they used a wide variety of definitions, complicating attempts to identify and compare risk factors for CKD across studies (1–8). A formal

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comparison of the association of risk factors, the most significant of which are diabetes and hypertension (9–11), under different definitions of incident CKD is needed.

We compare definitions of incident CKD using 9 years of follow-up data from the Atherosclerosis Risk in Communities (ARIC) Study. Four basic definitions of incident CKD are examined: 1) low estimated glomerular filtration rate (eGFR), 2) low and declining eGFR, 3) increase in serum creatinine, or 4) hospitalization or death with a kidney-related diagnosis. We compare agreement of these definitions in terms of case identification, incidence rates, and associations with known (e.g., diabetes (9, 10, 12), hypertension (9, 10, 13, 14), age (9, 11, 15)) and suspected (e.g., African-American race, male gender (16)) CKD risk factors.

MATERIALS AND METHODS

The ARIC Study is a prospective observational cohort of 15,792 self-reported white individuals and black individuals between the ages of 45 and 64 years (mean age, 54) at the baseline examination, recruited from 4 US communities (Forsyth County, North Carolina (10% black, 90% white); Jackson, Mississippi (100% black); suburban Minneapolis, Minnesota (100% white); and Washington County, Maryland (100% white)). Participants took part in examinations starting with a baseline visit (visit 1) between 1987 and 1989. Individuals had 3 follow-up examinations: visit 2 (1990–1992), visit 3 (1993–1995), and visit 4 (1996–1998), as well as annual follow-up telephone interviews between visits. Hospitalized events were ascertained continuously from enrollment to the present. These analyses assess data only through 1999. Details of the ARIC Study have been published elsewhere (17).

Included in the present analysis were all self-reported black participants and white participants with relevant covariate information who were free of prevalent CKD at baseline. We excluded participants who reported a race other than black or white ($n = 48$) and blacks from the Minnesota and Washington County study centers ($n = 55$) for consistency with the intended study design. In addition, those who were missing baseline serum creatinine values ($n = 149$), individuals with prevalent disease at baseline (here defined as all individuals with eGFR of <60 mL/minute/1.73 m^2 at visit 1; $n = 459$), those missing data on important covariates including hypertension and diabetes status, and those missing values for both low density lipoprotein cholesterol and high density lipoprotein cholesterol ($n = 208$) were also excluded. Within the aforementioned exclusions were also individuals with abnormally high baseline serum creatinine values (>2 mg/dL in men and >1.8 mg/dL in women). Analyses are based on the remaining 14,873 study participants.

Demographic (including self-reported race and gender) and health behavior data, medical history, and anthropometric measurements were obtained during each clinical examination. Blood was drawn at all clinic visits as described previously (18). Diabetes mellitus was defined as a fasting glucose of ≥ 126 mg/dL, nonfasting glucose of ≥ 200 mg/dL, self-reported physician diagnosis of diabetes mellitus, or use of oral hypoglycemic medication or insulin. Three seated blood pressure measurements (at each visit) were taken by certified technicians using a random-zero sphygmomanometer after 5 minutes of rest. The mean of the second and third readings was recorded. Enzymatic methods were used to obtain total plasma cholesterol, high density lipoprotein cholesterol, and triglycerides, while low density lipoprotein cholesterol was calculated from these by use of the Friedewald equation (19). Participants whose low density lipoprotein cholesterol concentration could not be calculated because of high triglyceride values (≥ 400 mg/dL, $n = 224$) were assigned the study population mean low density lipoprotein cholesterol value (137.7 mg/dL) (and were further adjusted on the basis of an indicator for this missingness). Smoking status was determined by self-reported cigarette smoking. Prevalent coronary heart disease was defined as a history of physician-diagnosed myocardial infarction, evidence of a prior myocardial infarction by electrocardiogram (presence of a major or minor Q-wave abnormality with T-wave or ST-segment abnormality), or a self-reported prior coronary revascularization procedure. Self-reported medication use was verified by bottle inspection.

A modified kinetic Jaffe method was used to measure serum creatinine at ARIC Study visit 1 (1987–1989), visit 2 (1990–1992), and visit 4 (1996–1998) (it was unavailable for visit 3). The serum creatinine concentration was corrected for interlaboratory differences, indirectly calibrated to the Cleveland Clinic measurement by subtraction of 0.24 mg/dL from the visit 1 and visit 2 values and the addition of 0.18 mg/dL to the visit 4 values, and then used to estimate the glomerular filtration rate (20, 21) with the 4-variable Modification of Diet in Renal Disease Study equation (22).

Incident CKD was defined in several different ways, as described in Table 1. First, low eGFR cases were defined as an eGFR falling below 60 mL/minute/1.73 m^2 at visit 2 or visit 4 among those with an eGFR of at least 60 mL/minute/1.73 m^2 at visit 1 (definition 1). Second, low and declining eGFR cases were defined as both an eGFR falling below 60 mL/minute/1.73m^2, as above, and a decrease in eGFR of at least 25% (definition 2). Third, creatinine rise cases were defined as an increase in serum creatinine of 0.4 mg/dL over the baseline at either visit 2 or visit 4 (definition 3) (1–3). Evaluation of the short-term variability of serum creatinine within ARIC Study participants revealed that 0.18 mg/dL (16 μmol/L) was the minimal real change in serum creatinine detectable with 95% confidence (using estimates of methodological and within-person variability of standard deviation = 0.05 mg/dL (4.4 μmol/L) and standard deviation = 0.04 mg/dL (3.5 μmol/L), respectively) (23). A value of twice this amount, or 0.4 mg/dL, was therefore used for long-term variation (24, 25). Fourth, hospitalization-based cases were defined by a kidney-related hospitalization, as captured by specified codes in the *International Classification of Diseases*, Ninth Revision (ICD-9), and cases of kidney-related death were captured by ICD-9 codes or *International Classification of Diseases*, Tenth Revision (ICD-10), codes through the last date of the 9-year follow-up visit (i.e., visit 4) (definition 4) (26).

Table 1. Description of Definitions[a] of Incident CKD in the Atherosclerosis Risk in Communities Study Population, United States, 1987–1999

Incident CKD Definition	Source of Information	Description
1. Low eGFR (eGFR, <60 mL/minute/1.73 m^2)	Follow-up visits	Among individuals with baseline eGFR of ≥ 60 mL/minute/1.73 m^2, a decline to an eGFR of <60 at the 3- or 9-year follow-up visit
2. Low and declining eGFR (eGFR, <60 mL/minute/1.73 m^2 and $\geq 25\%$ drop)	Follow-up visits	Among individuals with baseline eGFR of ≥ 60 mL/minute/1.73 m^2, a decline to an eGFR of <60 constituting a $\geq 25\%$ decline from the baseline eGFR to the 3- or 9-year follow-up visit
3. Serum creatinine rise (≥ 0.4 mg/dL)	Follow-up visits	Among men and women with baseline serum creatinine values of <2 and <1.8, respectively, a rise in serum creatinine of at least 0.4 mg/dL from baseline to the 3- or 9-year follow-up visit
4. CKD hospitalization or death	Clinical event, surveillance	Among all individuals, an ICD-9 or ICD-10 hospitalization or death code[b] involving a kidney diagnosis by the last (9-year follow-up) visit date

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICD-9 and ICD-10, *International Classification of Diseases,* Ninth and Tenth Revisions, respectively.

[a] To exclude individuals with prevalent disease at baseline, all individuals with an eGFR of <60 mL/minute/1.73 m^2 at visit 1 ($n = 453$) were excluded for all definitions.

[b] Includes hospitalizations (discharges or deaths) coded for chronic renal disease (ICD-9 codes 581–583 or 585–589; ICD-10 codes N03–N04, N19, N25–N27); hypertensive renal disease (ICD-9 code 403; ICD-10 code I12); hypertensive heart and renal disease (ICD-9 code 404; ICD-10 code I13); unspecified disorder of the kidney and ureter (ICD-9 code 593.9); diabetes with renal manifestations (ICD-9 code 250.4; ICD-10 codes E10.2, E11.2, E12.2, E13.2, E14.2, N08.3); kidney transplantation, renal dialysis, or adjustment/fitting of catheter (ICD-10 codes V42.0, V45.1, or V56; ICD-10 code N18; ICD-10 codes Z94, Z99.2, Z49.1, Z45.2); hemodialysis (ICD-9 code 39.95) or peritoneal dialysis (ICD-9 code 54.98), without acute renal failure (ICD-9 codes 584, 586, 788.9, 958.5; ICD-10 code N17) as the primary or secondary hospitalization code (26); and congenital kidney disease (ICD-9 codes 591, 593.7, 753; ICD-10 codes N07, N13.3, N13.7, Q60.6, Q61, Q63.8, Q63.9). Codes indicating acute renal failure were not included.

Hospitalizations were identified through active surveillance and included hospitalizations (discharges or deaths) coded for the following: chronic renal disease (ICD-9 codes 581–583 or 585–589; ICD-10 codes N03, N04, N19, N25–N27); hypertensive renal disease (ICD-9 code 403; ICD-10 code I12); hypertensive heart and renal disease (ICD-9 code 404; ICD-10 code I13); unspecified disorder of the kidney and ureter (ICD-9 code 593.9); diabetes with renal manifestations (ICD-9 code 250.4; ICD-10 codes E10.2, E11.2, E12.2, E13.2, E14.2, N08.3); kidney transplantation, renal dialysis, or adjustment/fitting of catheter (ICD-10 code V42.0, V45.1, or V56; ICD-10 codes N18, Z94, Z99.2, Z49.1, Z45.2); hemodialysis (ICD-9 code 39.95) or peritoneal dialysis (ICD-9 code 54.98) without acute renal failure (ICD-9 codes 584, 586, 788.9, 958.5; ICD-10 code N17) as the primary or secondary hospitalization code (26); and congenital kidney disease (ICD-9 codes 591, 593.7, 753; ICD-10 codes N07, N13.3, N13.7, Q60.6, Q61, Q63.8, Q63.9). Codes indicating acute renal failure were not included.

With regard to statistical analysis, follow-up time was calculated from the date of the first ARIC Study examination to the first date of CKD diagnosis (either visit 2 or visit 4) or the discharge date of a hospitalization or death with kidney disease. The visit date was used as a proxy for the event date for visit-based definitions. Participants who did not become a case were administratively censored at the first of time of death, withdrawal, or the date of visit 4 for creatinine- and eGFR-based case definitions. For ease of comparison of rates between incident CKD definitions, all definitions use rates with follow-up only as late as the last visit 4 (January 30, 1999).

Crude incidence rates of each incident CKD definition were calculated. Adjusted incidence rates for incident CKD and their 95% confidence intervals were computed by using Poisson multivariable regression. Fully adjusted multivariable models included age, gender, a race/study center combined variable, baseline eGFR, body mass index, hypertension status, diabetes status, prevalent coronary heart disease, smoking status, low density lipoprotein cholesterol and high density lipoprotein cholesterol, and (the natural log of) triglyceride concentrations as covariates. Incidence rate ratios for each of the covariates were compared among the incident CKD definitions by using bootstrapping methods, where each of the 1,000 iterations sampled the entire data set with replacement. We examined concordance of incident CKD case status identified by using the different definitions. All statistical analyses were conducted by using STATA (27, 28) or R statistical software.

Table 2. Baseline (Visit 1) Characteristics by Incident CKD Case Definition[a] in the Atherosclerosis Risk in Communities Study Population, United States, 1987–1999

Baseline (Visit 1) Characteristic (% or Mean (SD))	Overall[b] (n = 14,873)	Definition 1 (eGFR, <60 mL/minute/1.73 m^2) (n = 1,086)	Definition 2 (eGFR, <60 mL/minute/1.73 m^2, and ≥25% Drop) (n = 677)	Definition 3 (Creatinine Rise) (n = 457)	Definition 4 (CKD Hospitalization or Death) (n = 163)
Age, years	54 (5.7)	57 (5.6)	57 (5.5)	56 (5.6)	56 (5.5)
Black race, %	25.8	19.2	22.9	41.6	41.1
Male, %	45.22	41.4	40.5	54.7	48.5
Serum creatinine, mg/dL	0.84 (0.18)	0.96 (0.18)	0.90 (0.17)	0.88 (0.21)	0.91 (0.23)
eGFR, mL/minute/1.73 m^2	94 (20)	77 (14)	83 (14)	96 (26)	91 (23)
Mildly decreased (60–89 mL/minute/1.73 m^2) GFR, %	51.0	87.2	79.5	50.8	59.5
Diabetes, %	11.4	17.4	21.6	29.8	55.2
Prevalent coronary heart disease, %	4.6	7.2	8.6	9.2	9.8
History of myocardial infarction, %	3.7	6.4	7.5	8.1	8.6
Hypertension, % (stage 1 or stage 2 or taking antihypertensive medications)	33.9	50.0	53.6	56.9	62.6
Hypertension medications, %	24.4	37.1	39.1	40.5	49.7
Systolic blood pressure, mm Hg	121 (19)	127 (21)	129 (23)	132 (23)	132 (21)
Diastolic blood pressure, mm Hg	74 (11)	75 (12)	75 (12)	77 (13)	76 (14)
Blood pressure category, %					
Normal	48.1	35.3	33.1	28.0	23.3
Prehypertension	34.7	36.8	35.3	35.5	40.5
Stage 1 hypertension	12.8	20.1	21.6	25.4	27.0
Stage 2 hypertension	4.4	7.8	10.0	11.2	9.2
Smoking status, %					
Current	26.3	18.5	20.5	23.0	33.1
Former	32.3	35.0	35.8	35.9	29.5
Never	41.4	46.5	43.7	41.1	37.4
Body mass index, kg/m^2	27.6 (5.3)	28.1 (5.0)	28.2 (5.2)	29.1 (5.5)	30.3 (6.5)
Total cholesterol, mg/dL	215 (42)	222 (45)	222 (47)	221 (50)	225 (48)
High density lipoprotein cholesterol, mg/dL	52 (17)	50 (17)	50 (17)	48 (15)	45 (16)
Low density lipoprotein cholesterol, mg/dL	138 (39)	142 (41)	142 (42)	142 (44)	143 (38)
Triglycerides, mg/dL	131 (90)	150 (99)	154 (105)	159 (115)	199 (178)

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; SD, standard deviation.

[a] The definitions are not mutually exclusive; individuals who are cases by definition 2 are all, by definition, included in definition 1; overlap exists in other categories as detailed in Figure 2.

[b] The following characteristics had missing values for overall: systolic blood pressure (n = 3), diastolic blood pressure (n = 2), smoking status (n = 9), body mass index (n = 12), and low density lipoprotein cholesterol (n = 224).

RESULTS

Study sample

Table 2 shows characteristics of the study population overall and by each of the (not mutually exclusive) incident CKD definitions. At baseline, persons who subsequently met any of the incident CKD definitions were, on average, older, had a higher mean serum creatinine level, had a lower mean eGFR, were more likely to have several comorbidities, and had a higher mean blood pressure level and worse lipid profiles.

Follow-up and outcomes of participants

The ARIC Study had excellent follow-up over time (Figure 1), with over 90% follow-up between sequential visits. Follow-up until the last date of the 9-year follow-up visit in 1999 yielded 1,086 low eGFR (definition 1) cases over

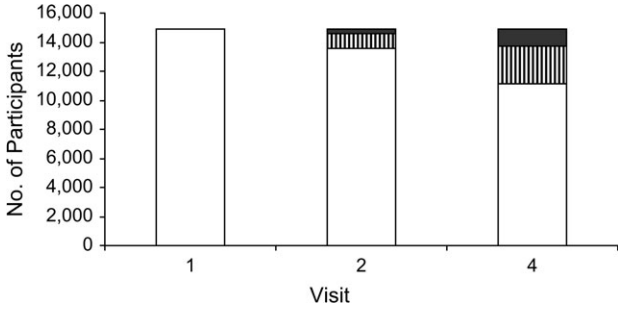

Figure 1. Follow-up and sample size by visit in the Atherosclerosis Risk in Communities Study, United States, 1987–1999. The number of participants after initial exclusions were made is represented. White bars represent the number present at the visit; striped boxes, the (cumulative) number who died prior to the visit; and black boxes, the number who were absent from the visit. For visit 1, 14,873 individuals were present; for visit 2, 13,586 were present, 1,023 had died prior, and 264 were absent; for visit 4, 11,101 were present, 2,591 had died prior, and 1,181 were absent. Visit 3 was not included in the figure, because serum creatinine measurements were not available at that time.

a median of 8.8 years (104,653 person-years). Of these, the decrease in eGFR was $\geq$25% from the baseline value (definition 2) in 677 participants over a similar median follow-up time (101,172 person-years). There were 457 serum creatinine rise cases (definition 3) over a median of 8.9 years (106,196 person-years). The hospitalization-based definition (definition 4) yielded fewer cases with similar follow-up time: 163 cases after a median follow-up of 8.9 years (132,103 total person-years).

The individuals qualifying as cases for the 4 incident CKD definitions are partly overlapping (Figure 2). Of the 1,290 participants who met any definition, the largest group, 1,086 participants, met the low eGFR definition. Of these, 403 met only this case definition, 309 also experienced a decline in eGFR of $\geq$25% from baseline, while another 316 had low eGFR as well as both declining eGFR and a serum creatinine rise. Hospitalization-based cases were less common. Among 163 hospitalization-based cases, 104 met no other case definition. Thirty of these additional cases attended no follow-up visit after baseline, making it impossible for them to meet other definitions of incident CKD, while an additional 61 did not attend the 9-year follow-up visit, limiting their creatinine follow-up to only 3 years.

Figure 3 shows the percent change in eGFR from baseline until the time of incident CKD among those who are eGFR-decline and serum creatinine-increased cases.

The incidence rates of incident CKD were highest for low eGFR, followed by the low and declining eGFR, serum creatinine rise, and lastly, hospitalization-based definitions, with 10.4, 6.7, 4.3, and 1.2 cases occurring per 1,000 person-years, respectively (Table 3).

Risk factor associations

Stratification by key risk factors (age, race, gender, diabetes status, hypertension status), as seen in Table 3,

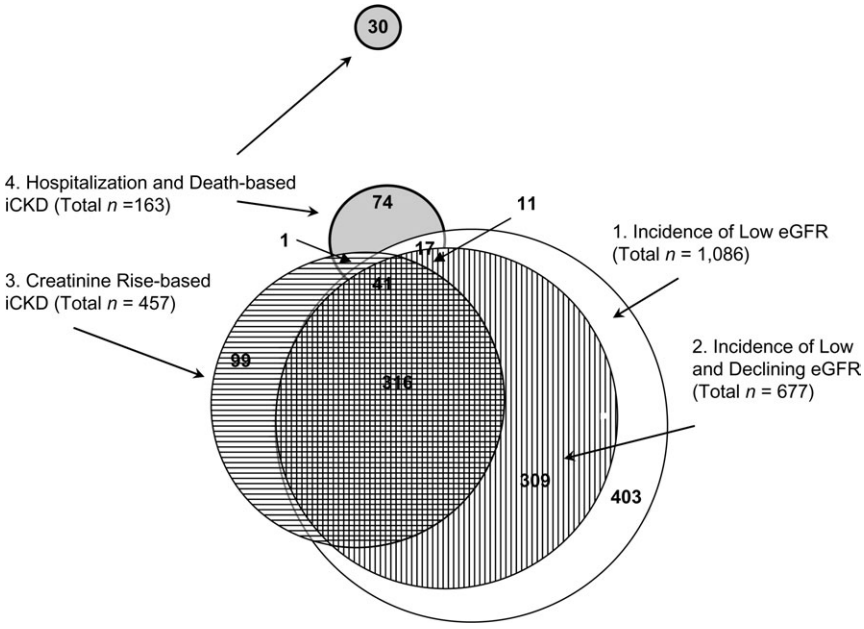

Figure 2. Concordant and discordant occurrence of incident chronic kidney disease (iCKD) in the Atherosclerosis Risk in Communities Study population, United States, 1987–1999, by case definition. Definition 1 is represented by the largest, empty, outer circle; definition 2, by the inner circle with vertical lines; definition 3, by the leftmost circle with horizontal lines; and definition 4, by the 2 smallest gray circles at the top. Of the 74 hospitalization- and death-based cases who do not overlap with any other case definition, only 12 had both 3- and 9-year follow-up measures, while 60 had follow-up serum creatinine measured only at the 3-year follow-up visit, and 2 had only a 9-year follow-up measure. The 30 cases in a separate circle did not attend any follow-up visits. eGFR, estimated glomerular filtration rate.

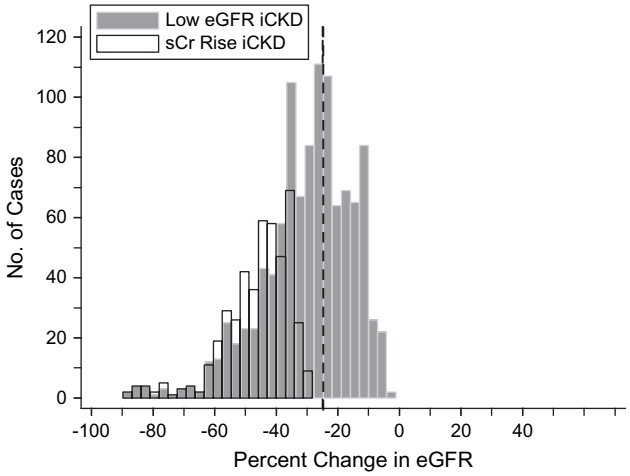

Figure 3. Distribution of percent change in estimated glomerular filtration rate (eGFR) from baseline to the time of incident chronic kidney disease (iCKD) in the Atherosclerosis Risk in Communities Study population, United States, 1987–1999. The change in eGFR from baseline until the time of iCKD is represented here, where a negative change reflects a decrease in eGFR, and a positive change represents an increase. Histograms represent the distribution of percent change in eGFR among those who were low eGFR (definition 1) for gray bars and creatinine rise (definition 3) iCKD cases for empty bars. The black, dashed, vertical line represents the cutoff of a 25% decline in eGFR. sCr, serum creatinine.

compares risk factor associations. The rank order of incidence rates across all incident CKD definitions remained consistent with overall rates. Participants at least 55 years of age, those with diabetes, and those with hypertension had higher crude incident CKD incidence rates compared with their counterparts. Blacks had a higher incidence than did whites for serum creatinine rise and hospitalization-based definitions but had a lower incidence based on low eGFR. The incidence of low and declining eGFR cases, by definition 2, resulted in similar incidence rates for blacks and whites. Women had a higher incidence than did men for both eGFR-based definitions, but they had a lower incidence for creatinine-based cases. Hospitalization-based cases resulted in similar incidence rates for women and men (Table 3).

After adjustment for potential confounders, including baseline eGFR, several differences remained (Table 4). Older age was strongly associated with visit-based cases but not with hospitalization-based cases ($P = 0.02$) (Table 4). Male sex was inversely associated with eGFR-based cases, positively associated with creatinine-based cases, and not significantly associated with hospitalization-based cases. Diabetes was least strongly associated with eGFR-based cases and most strongly associated with hospitalization-based cases. For individuals with, compared with those without, diabetes for the risk of hospitalization-based incident CKD, the incidence rate ratio was 6.30 (95% confidence interval (CI): 4.43, 8.95); compared with the eGFR-based definitions, the incidence rate ratios were 1.47 (95% CI: 1.23, 1.74) and 1.82 (95% CI: 1.49, 2.23) for definitions 1 and 2, respectively. Hypertension was associated with incident CKD in all definitions but did not statistically differ between any pair ($P \geq 0.31$ for all pairwise comparisons) of incident CKD definitions. Black race was associated most strongly with creatinine-based cases and least strongly associated with eGFR-based cases, with hospitalization-based cases showing intermediate results, with a relative incidence rate ratio (creatinine based/eGFR based) = 1.9 ($P < 0.001$).

To account for differences in both race and center, a combined variable was created, resulting in inconsistent associations between black race and incident CKD in adjusted analyses. However, when looking at race and center separately, an increased risk of (all definitions of) incident CKD was associated with black race, the Mississippi field center (100% black, $n = 3{,}384$), or both (results not shown).

Sensitivity analyses (results not shown) varied the cutoff for serum creatinine rise around 0.4 mg/dL and showed that a lower cutoff of a rise of 0.3 mg/dL (yielding 890 cases) generally resulted in lower relative risks with smaller confidence intervals. Conversely, a higher cutoff of a rise of 0.5 mg/dL (yielding only 224 cases) resulted in higher relative risks but wider confidence intervals. Associations had similar trends across all cutoffs and similarly compared with other definitions.

DISCUSSION

Because of the lack of a standard definition of incident CKD for research purposes, investigators have used widely varying criteria (1–3, 13, 24, 25, 29–32). This comparison of several definitions (Table 1) of incident CKD within one study population elucidates some of the distinctions among case definitions in terms of incidence rates and associations with risk factors (e.g., diabetes (9, 10, 12), African-American race, male gender (16)). Most major risk factor associations were robust in terms of direction and statistical significance across the 4 definitions explored. However, the magnitude of the associations varied substantially for the majority of the risk factors. Surprisingly, the direction and statistical significance of the association with incident CKD changed across the different definitions for race and sex. The definition based on clinical events (definition 4) was the most stringent (low sensitivity) but captured individuals with the greatest number of comorbidities.

Incidence and risk factor associations

We observed various degrees of association between risk factors and each incident CKD outcome. Age and diabetes status were associated in the same direction, but the strength of the association varied depending on the definition of incident CKD used. Adjusted analyses showed inconsistent associations between race/center and incident CKD. Because race and center are so highly correlated, they were combined, resulting in associations that were not statistically significant, likely due to a lack of power after stratification (a total of only 454 blacks were in the North Carolina center). Associations found among blacks in the Mississippi center are likely to be more reliable ($n = 3{,}384$).

Table 3. Incidence of CKD Cases by Demographics: Follow-up in the Atherosclerosis Risk in Communities Study, United States, 1987–1999[a,b]

Sample	Definition 1 (eGFR, <60 mL/minute/1.73 m^2)			Definition 2 (eGFR, <60 mL/minute/1.73 m^2, and ≥25% Drop)			Definition 3 (Creatinine Rise)			Definition 4 (CKD Hospitalization or Death)		
	Incidence/1,000 Person-Years	95% Confidence Interval	*P* Value	Incidence/1,000 Person-Years	95% Confidence Interval	*P* Value	Incidence/1,000 Person-Years	95% Confidence Interval	*P* Value	Incidence/1,000 Person-Years	95% Confidence Interval	*P* Value
Overall	10.38	9.78, 11.01		6.69	6.21, 7.22		4.30	3.93, 4.72		1.23	1.06, 1.44	
Baseline age, years												
≥55	15.71	14.62, 16.88	<0.001	9.95	9.08, 10.91	<0.001	5.93	5.28, 6.66	<0.001	1.60	1.31, 1.95	0.001
≤54	6.00	5.40, 6.67		3.99	3.50, 4.55		2.96	2.55, 3.44		0.93	0.73, 1.18	
Gender												
Men	9.58	8.74, 10.50	0.021	5.94	5.28, 6.69	0.020	5.28	4.66, 5.97	<0.001	1.34	1.07, 1.67	0.405
Women	11.02	10.20, 11.92		7.32	6.64, 8.07		3.52	3.07, 4.03		1.15	0.93, 1.42	
Race												
Blacks	8.87	7.74, 10.16	<0.001	6.87	5.87, 8.04	0.446	8.02	6.96, 9.25	<0.001	1.99	1.56, 2.53	<0.001
Whites	10.82	10.12, 11.56		6.64	6.09, 7.23		3.23	2.87, 3.65		0.98	0.80, 1.19	
Diabetes												
With	18.89	16.38, 21.79	<0.001	15.17	12.90, 17.84	<0.001	13.37	11.30, 15.81	<0.001	6.27	5.10, 7.71	<0.001
Without	9.48	8.88, 10.12		5.80	5.33, 6.32		3.34	3.00, 3.73		0.62	0.49, 0.78	
Blood pressure												
Hypertensive	16.72	15.37, 18.19	<0.001	11.50	10.38, 12.75	<0.001	7.83	6.93, 8.84	<0.001	2.31	1.90, 2.80	<0.001
Normotensive	7.52	6.92, 8.18		4.51	4.04, 5.04		2.70	2.35, 3.10		0.69	0.54, 0.89	

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

[a] The number of events/total number of individuals was 1,086/13,744 for definition 1, 677/13,744 for definition 2, 457/13,744 for definition 3, and 163/14,873 for definition 4.

[b] *P* values, determined through the likelihood ratio test, are given for interaction by strata.

Table 4. Comparison of Incidence Rate Ratios for Established and Novel Risk Factors Across 4 Incident CKD Case Definitions[a] in the Atherosclerosis Risk in Communities Study, United States, 1987–1999

Risk Factor	Definition 1 (eGFR, <60 mL/minute/1.73 m^2)			Definition 2 (eGFR, <60 mL/minute/1.73 m^2, and ≥25% Drop)			Definition 3 (Creatinine Rise)			Definition 4 (CKD Hospitalization or Death)		
	Incidence Rate Ratio	95% Confidence Interval	Differences[b]	Incidence Rate Ratio	95% Confidence Interval	Differences[b]	Incidence Rate Ratio	95% Confidence Interval	Differences[b]	Incidence Rate Ratio	95% Confidence Interval	Differences[b]
≥55 years of age	1.56	1.37, 1.79		1.68	1.42, 1.99		1.68	1.38, 2.05		1.17	0.85, 1.63	
Male gender	0.79	0.69, 0.91	–, –, 3	0.75	0.62, 0.89	–, –, 3	1.44	1.17, 1.78	1, 2, –, –	1.09	0.77, 1.54	
Diabetes	1.47	1.23, 1.74	–, 2, 3, 4	1.82	1.49, 2.23	1, –, –, 4	2.16	1.72, 2.70	1, –, –, 4	6.30	4.43, 8.95	1, 2, 3, –
Hypertension	1.55	1.36, 1.77		1.81	1.53, 2.14		1.70	1.39, 2.09		1.71	1.21, 2.42	
Prevalent coronary heart disease	1.15	0.91, 1.46		1.44	1.09, 1.90		1.36	0.98, 1.89		1.14	0.67, 1.95	
Body mass index	1.00	0.98, 1.01		0.99	0.98, 1.01		1.01	0.99, 1.02		1.03	1.00, 1.06	
Smoking												
Never	1.00			1.00			1.00			1.00		
Former	1.02	0.89, 1.17		1.11	0.93, 1.33		1.04	0.83, 1.30		1.03	0.69, 1.54	
Current	0.92	0.78, 1.09		1.03	0.83, 1.26		0.95	0.74, 1.22		1.73	1.17, 2.54	
High density lipoprotein cholesterol[c]	21.52	21.43, 21.63		21.59	21.46, 21.71	–, –, 3, –	21.43	20.28, 20.59	–, 2, –, –	21.46	21.18, 21.74	
Log triglyceride[c]	0.83	0.71, 0.97		0.89	0.74, 1.08		0.91	0.72, 1.14		0.86	0.58, 1.26	
eGFR[c]	19.18	19.08, 19.28	–, 2, 3, 4	19.69	19.75, 19.96	1, –, 3, 4	20.60	20.50, 20.69	1, 2, –, 4	20.25	20.08, 20.42	1, 2, 3, –
White race, Forsyth County, North Carolina	1.00			1.00			1.00			1.00		
White race, Minneapolis, Minnesota	0.91	0.77, 1.08		0.95	0.76, 1.18		0.92	0.68, 1.26		0.95	0.56, 1.61	
White race, Washington County, Maryland	1.01	0.86, 1.19		1.08	0.88, 1.34		1.03	0.77, 1.38		1.12	0.68, 1.82	
Black race, Forsyth County, North Carolina	0.82	0.51, 1.31		0.55	0.28, 1.09		0.92	0.47, 1.79		2.09	0.99, 4.41	
Black race, Jackson, Mississippi	1.13	0.92, 1.38	–, –, 3, –	1.18	0.92, 1.52	–, –, 3, –	2.10	1.57, 2.80	1, 2, –, –	1.57	0.95, 2.57	

Abbreviations: CKD, chronic kidney disease, eGFR, estimated glomerular filtration rate.

[a] Models included all the covariates seen here and were also adjusted for low density lipoprotein cholesterol.

[b] $P < 0.01$ for 2-sided differences (in the incidence rate ratio of the given risk factor) from the other incident CKD outcomes corresponding to the definition number indicated; for example, the incidence rate ratio comparing male with female gender for the risk of incident CKD by definition 1 is different from the risk of incident CKD by definition 3 at the $P < 0.01$ level (likewise, as indicated, the risk is different for incident CKD by definition 2 than it is for definition 3).

[c] The incidence rate ratios given are per interquartile range: for high density lipoprotein cholesterol, 39.48–61.00 mg/dL; for log triglyceride, 4.36–5.05 mg/dL; and for eGFR, 81.82–102.38 mL/minute/1.73 m^2.

Hypertension and higher plasma triglycerides were positively associated with CKD to the same degree, regardless of which definition was used. Gender was associated with CKD in different directions, depending on the definition. Other risk factors, such as baseline eGFR and smoking status, were associated with some definitions of CKD but not others. Although these results confirm that well-known risk factors are consistently associated with incident CKD across several definitions, they also emphasize the influence of the study population and the importance of incident CKD definition choice when studying novel risk factors of CKD.

Age. Older age was a strong risk factor for all 3 visit-based case definitions, but it was not significantly associated with CKD hospitalization or death in middle age. As no hospital-based laboratories reported eGFR before 1999, this may be due to some underdiagnosis of CKD based on serum creatinine among older individuals.

Gender. With full adjustment for known risk factors and baseline eGFR, the associations with gender varied across definitions. Definition 3 identified male sex as a risk factor for incident CKD, whereas definitions 1 and 2 identified male sex as protective. The nonlinear relation between serum creatinine and eGFR may partially explain this apparent discrepancy. On average, men have more muscle mass and therefore higher serum creatinine than women. A similar increase in serum creatinine equates to a smaller proportional decrease in eGFR for a man than a woman. It is possible that differential errors in glomerular filtration rate estimates made using the Modification of Diet in Renal Disease Study equation also play a role.

Race. Similarly, blacks, compared with whites, had a higher incidence of creatinine rise ($P < 0.001$) but only slightly higher rates of eGFR-based cases ($P = 0.23$). Blacks in our study had a slightly higher mean baseline serum creatinine concentration (0.86 vs. 0.84 mg/dL) but with 40% greater variance compared with whites. On average, blacks experienced greater changes in serum creatinine between visits 1 and 4. Both absolute and proportional increases in serum creatinine were slightly larger among blacks compared with whites, while proportional decreases were the same for both races. A similar absolute increase in serum creatinine corresponds to a smaller decrease in eGFR in a black individual than in a white individual (likely due to differences in muscle mass).

Although the higher incidence of creatinine-based cases in blacks compared with whites is likely attributable to some true increased risk, the higher incidence of hospitalization-based cases relative to visit-based cases among blacks compared with whites is likely also a function of other mechanisms. Blacks have a higher prevalence of some comorbidities, including hypertension, stroke (33), and diabetes (33, 34), and in our cohort, they have a greater risk of hospital admission (data not shown). This difference may affect hospital coding for CKD. There is also evidence for physician diagnostic preference by race (35). Blacks also were more likely to be lost to follow-up (16.4% and 38.3% of blacks were missing follow-up serum creatinine values at visits 2 and 4, respectively, compared with 6.3% and 21.6% of whites). These differential losses may substantially decrease the precision of visit-based definitions to identify cases among blacks. This phenomenon occurred despite the ARIC Study's having higher follow-up rates than many prospective studies.

Diabetes. Diabetes also was more strongly associated with the creatinine-based cases (definition 3) than the eGFR-based cases (definitions 1 and 2). This difference may be explained by an underestimate of incident CKD cases as identified by definitions 1 and 2. Early kidney disease can be associated with hyperfiltration preceding the development of albuminuria and manifest diabetic nephropathy, in which eGFR is increased (36). Kidney disease in individuals in the early stages of diabetic nephropathy may therefore not be fully captured with the eGFR-based case criteria. However, although this is a relatively well-accepted chain of events among type 1 diabetics (36), the role of hyperfiltration in individuals with type 2 diabetes (representing 90%–95% of diabetes cases (34) and the vast majority of ARIC Study cases) is still debated (36).

More hospitalization-based cases among individuals with diabetes also may be explained by more comorbidities and hospital admissions (34), a lower threshold for development of renal failure and end-stage renal disease in diabetics during acute illnesses, and, potentially, a differential diagnosis rate with a smaller proportion of CKD being missed in the presence of diabetes (9, 10), inflating already increased rates of CKD in this risk group. Greater risk associated with diabetes comparing hospital-based cases with visit-based cases may be not only related to increased risk and increased diagnosis but also likely to have the opposite effect on visit-based case status. Individuals with diabetes are less likely to become a visit-based case compared with individuals without diabetes, as more are lost to follow-up and no longer eligible to be a visit-based case. Among individuals with diabetes at visit 1, 15.7% and 41.2% were missing follow-up serum creatinine values at visits 2 and 4, respectively, compared with 8.1% and 23.9% of individuals without diabetes at baseline.

Agreement of incident CKD cases

All creatinine rise-based cases experienced a decrease in eGFR of at least 28.2% (and thus met the criterion of an eGFR fall of $\geq$25%). However, there are creatinine rise-based cases whose eGFR did not fall below 60 ml/minute/1.73 m^2 ($n = 100$). This could occur among participants who started with higher eGFRs (i.e., one whose eGFR and serum creatinine changed, respectively, from visit 1 to visit 2 from 159 to 82 mL/minute/1.73 m^2 and from 0.66 to 1.16 mg/dL), as well as among participants starting with normal eGFRs (i.e., one whose eGFR and serum creatinine changed, respectively, from visit 1 to visit 2 from 113 to 66 mL/minute/1.73 m^2 and from 0.76 to 1.18 mg/dL).

Limitations

Our study is limited by the lack of a direct measure of kidney function. No ''gold standard'' diagnosis was available and, thus, we lacked estimates of sensitivity and specificity of individual incident CKD definitions. Direct measurement of kidney function is impractical in large

cohorts, and most recent studies have used the estimated glomerular filtration rate, as was done in this study. Although losses to follow-up are an ongoing concern in all prospective studies with lengthy follow-up, the ARIC Study had higher retention than most prospective studies: Over the length of the study, 91%, 90%, and 90% of participants returned from one visit to the next 3-year follow-up. Attention was paid to attempt consistent serum creatinine calibration across visits in the ARIC Study (20), but this is difficult and can impact the overall incidence rate of laboratory-diagnosed CKD. Only events occurring in acute-care hospitals were investigated. Events occurring in other institutions providing medical care, such as nursing homes, were not. Hospital admissions took place across several hospitals, so consistency of use of diagnostic codes is uncertain. Moreover, the use of hospital diagnostic codes to define CKD is not well studied; those that have carried out validation studies have shown mixed results across different facilities (though all report excellent specificity) (37, 38). We did not have data on baseline albuminuria and, therefore, cannot address the possibility that some participants had prevalent stage 1 or stage 2 CKD at baseline (39). Finally, we focused on a few published or proposed alternative definitions of CKD incidence but cannot cover all possible definitions. In this case, we have focused on those definitions that are most relevant to large research studies, which typically have few and infrequent measures at set time points, namely, definitions including threshold criteria. Using case definitions based on a measurement taken at a single time point or the change between infrequent measurements can be prone to consequences including the potential for measurement error, regression to the mean, and heterogeneity of cases, particularly between those far from and close to the set threshold.

Implications

Our results highlight the complementary nature of visit-based definitions of CKD incidence and CKD codes in hospitalizations and deaths, since individuals in the latter group are less likely to attend visits despite, or because of, having more severe CKD. We highlight differences among 3 visit-based uses of serum creatinine, showing that most risk factors evidence similar direction of association. However, the magnitude can vary, particularly for diabetes, and the direction is susceptible to change for sex and race. On the basis of these findings, it is not possible to conclude that one single definition is universally better than the others. We have highlighted some of the critical differences of each and bring investigators' and readers' attention to the advantages and disadvantages of studying outcomes defined by measures taken at study visits or events between visits. We have shown the importance of including event-based data, along with visit-based information, as definitions based solely on measures taken at visits miss a substantial number of cases that are lost to follow-up. Along with consideration of the challenges and rationale of optimizing sensitivity and specificity of any outcome, these data can help in the design and analysis of future studies of CKD incidence, as well as the interpretation of different results from studies using different CKD incidence definitions (1–8).

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