Invited Commentary: Defining Incident Chronic Kidney Disease in Epidemiologic Study Settings

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Chronic kidney disease affects an estimated 31 million Americans and potentially poses a significant global health and socioeconomic crisis. Chronic kidney disease can be treated if patients are identified early enough in the evolution of their kidney disease. However, in order for this to occur, suitable definitions of what is meant by “chronic kidney disease” need to be identified. In clinical practice, prevalent chronic kidney disease is diagnosed in a patient on the basis of the presence of persistent albuminuria and/or reduced glomerular filtration rate. However, it is unclear how to best define an incident of chronic kidney disease when the definition relies on the need for a patient to be seen multiple times over an extended period of time. In this issue of the Journal, Bash et al. (Am J Epidemiol. 2009;170(4):414–424) have compared 4 different definitions of incident chronic kidney disease and their agreement, incident rates, and association with known risk factors. This study explores an extremely important topic for longitudinal epidemiology studies of chronic kidney disease.

Disease definition is the foundation of many research studies, especially those concerned with understanding rare and complex diseases in the community. For these types of studies, “disease” is used to define a group of unrelated individuals who share a homogeneous phenotype from those who do not. The assignment of an individual to a “disease” phenotypic group can be used to identify genetic, epigenetic, or biochemical causes of disease that can lead to novel therapeutic targets. Chronic kidney disease (CKD) can be both “rare,” where a specific and classifiable glomerulonephritic lesion cosegregates with disease in families, and “complex,” where there is a group of diabetic patients with impairment of renal function. Whatever the underlying cause, CKD has increased in prevalence within the United States by 20%–25% from the 1988–1994 period of the National Health and Nutrition Examination Survey (1, 2) and affects an estimated 31 million Americans (1). Worldwide, noncommunicable diseases pose the greatest threat to public health and health budgets (3), and CKD is known to multiply the risk for detrimental outcomes in patients with noncommunicable disease, such as those with cardiovascular issues (4). If detected early enough, CKD can be treated, and this can reduce both the risk of kidney disease complications (such as cardiovascular events) in patients and also health-care costs.

Most large, prospective investigations of phenotypic patient data have identified incident CKD in patients on the basis of serum creatinine and International Classification of Diseases (ICD) codes during administration of medical care (5–9). However, a formal comparison of known risk factors for CKD (such as diabetes) cannot be done at present as previous studies have used a wide variety of definitions for CKD. A study is needed in the field that compares several definitions of incident CKD in one population, as this type of analysis should help to identify some of the distinctions among case definitions of incident CKD in relation to their incidence rates and association with risk factors.

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICD, International Classification of Diseases.

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This is the objective of the analysis conducted by Bash et al. (10). These authors use data derived from 4 distinct US clinical centers comprising a total of 14,873 available Caucasian and African-American patients and originally collected under the auspices of the Atherosclerosis Risk in Communities (ARIC) Study. The patients visited their respective clinics 4 times for the purpose of the ARIC Study over a 9-year period, and serum creatinine was measured on 3 of these visits: visit 1 (1987–1989), visit 2 (1990–1992), and visit 4 (1996–1998). The ARIC Study had excellent retention over time, with 91%, 90%, and 90% of participants returning from one visit to the next.

The authors used 4 definitions of incident CKD, these being a low estimated glomerular filtration rate (eGFR) (<60 mL/minute/1.73 m²) (definition 1); a low and declining (≥25%) eGFR (definition 2); an increase in serum creatinine (≥0.4 mg/dL) (definition 3); and/or CKD-related hospitalization or death (definition 4). Obviously, definitions 1–3 are based on a serum creatinine measure, while definition 4 is more concerned with clinical events.

Of the 14,873 available patients, 1,290 met at least 1 of the 4 incident CKD definitions used (although there was overlap between case definitions as they were not mutually exclusive). Most of these patients (n = 1,086) had a low eGFR (definition 1), and the rates of incident CKD were highest for low eGFR (definition 1). Definition 4 (CKD-related hospitalization or death) captured the least number of incident CKD cases, although these participants had the greatest number of comorbidities. Risk factor associations (diabetes, African-American race, and male gender) were consistent across the 4 definitions for hypertension and lipids. Individuals over the age of 55 years, those with diabetes, and those with hypertension had a higher incidence of incident CKD (which is expected from previous studies (5–9)). However, the magnitude of association between these risk factors and incident CKD varied across the 4 different definitions for race and sex. For instance, in a comparison with Caucasian Americans, African Americans experienced a higher incidence of creatinine rise (definition 3) but a diminished number of cases based on eGFR (definition 1 and definition 2). The authors found that both absolute and proportional increases in serum creatinine were slightly larger in African Americans compared with the Caucasians studied. However, proportional decreases were the same for both ethnicities. As the authors correctly point out, a similar absolute increase in serum creatinine corresponds to a smaller decrease in eGFR in African Americans compared with Caucasians, which they suggest is likely due to a difference in muscle mass between the 2 ethnicities. In relation to gender, the authors found that serum creatinine rise (definition 3) identified males at a higher risk of having incident CKD, while definitions 1 and 2 (concerned with eGFR measures) did not. The authors have also correctly stated that men (on average) have greater muscle mass compared with women and, therefore, have higher serum creatinine levels. Thus, a similar increase in serum creatinine means that a man will have a smaller decrease in GFR compared with a woman.

Bash et al. (10) have found that there is no way to conclude that one definition of incident CKD is better than another at identifying cases, as complex issues arise when race and gender are considered in a study population while attempting to define incident CKD on the basis of serum creatinine measures. In the Caucasian population, one could use definitions based on eGFR (definitions 1 and 2) that will define the greatest number of individuals with incident CKD. However, if definitions 1 and 2 are used in the African-American population, most cases of incident CKD will be missed. Also complicating definitions of incident CKD are ICD codes (definition 4). If the codes are used alone, Bash et al. (10) found that a smaller number of incident CKD cases will be identified but that the individuals captured will be those with the greatest number of comorbidities. It must be pointed out, though, that the ICD codes vary from version to version, and this may subject a study to a higher rate of phenotype error; thus, a formal analysis of ICD code use in an epidemiologic study setting seems warranted.

When defining incident CKD, investigators perhaps should include event-based measures along with visit-based information although, according to the work undertaken by Bash et al. (10), the ethnicity and sex of the study population and choice of incident CKD definition can greatly impact whether a participant is considered to have incident CKD. This is important because, if only visit-based data are used to define incident CKD, a great number of patients will be missed that may be lost due to follow-up.

The study by Bash et al. (10) illustrates that defining incident CKD is vastly more complex than defining prevalent CKD, and phenotyping issues for this disease will further complicate both genetic efforts to understand the molecular aspects of incident CKD and preventative medicine. Bash et al. (10) have thus shown that, unfortunately, there may be not be an easy solution nor best way to define “incident CKD.”

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1. US Renal Data System. USRDS 2008 Annual Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the


